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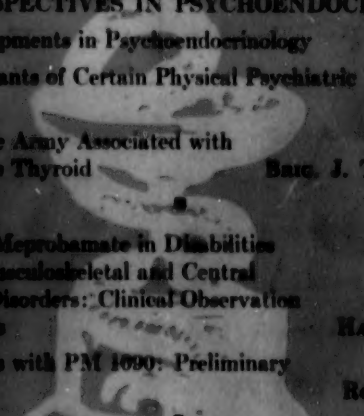

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FELIX MARTI-IBAÑEZ, M.D., Editor

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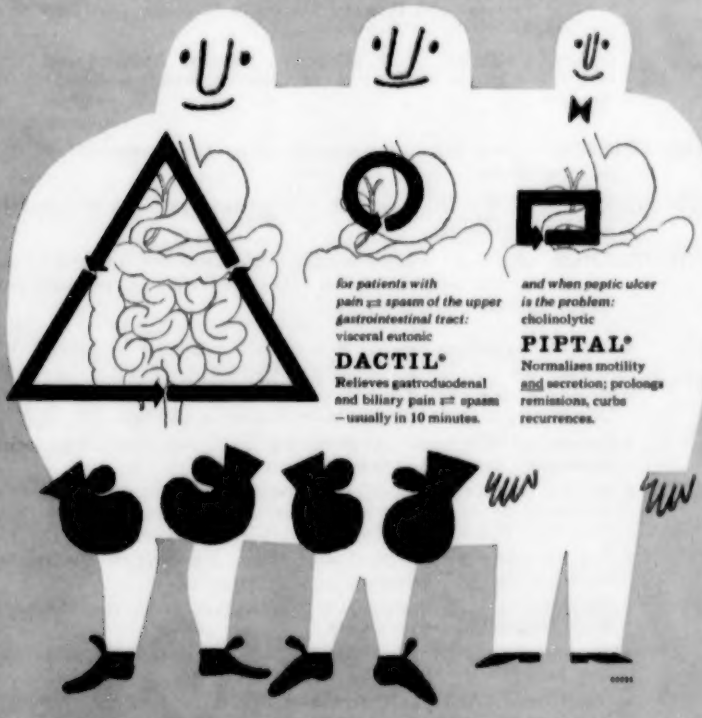

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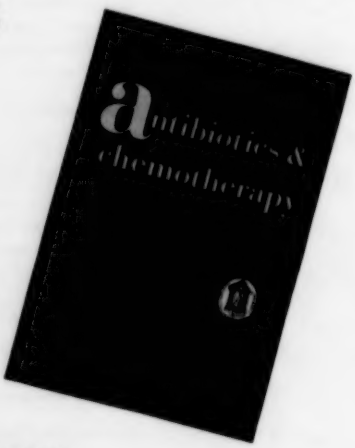

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NEW PERSPECTIVES IN PSYCHOENDOCRINOLOGY

Some Recent Developments in Psychoendocrinology*†

Dalton E. Sands, F.R.C.P. (Edin.), D.P.M.

PHYSICIAN SUPERINTENDENT, ST. EBBA'S HOSPITAL, EPSOM, ENGLAND;
ASSOCIATE PSYCHIATRIST, KING'S COLLEGE HOSPITAL, LONDON, ENGLAND

There are many signs of an intimate relationship between endocrine glands, as parts of the whole psychosomatic organization, and mental disorder, but so far, evidence of any etiological relationship has been indefinite. Henderson and Gillespie point out that we know that mental disease commonly breaks out at puberty, pregnancy, or the menopause, that the thought content of a psychosis may often be sexually colored, and that disturbance of the sexual functions and paresthesias are common symptoms. Menstruation with tension and other neurotic symptoms has been much discussed. It is known that relief of the neurotic tension symptoms can be assisted by endocrine means with progesterone, even if psychologic factors also need attention, as work by Greene et al has shown. However, several factors showed that it might be worth while to re-examine this relationship that we know must exist between the nervous and endocrine systems, and to see if unifying concepts can be worked out, even if so far we have been unable to understand the detail of the mechanisms involved.

Improvement in some endocrinological laboratory methods has widened considerably the scope of investigations and of diagnostic possibilities. I^{131} tracer methods now play an important part in the investigation of the thyroid function, and the uptake of the isotope has been seen to vary in relation to changes in the mental state. It has also become evident that the basal metabolic rate, while usually in agreement with the results of I^{131} tracer investigation, is not always so,

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* Based on a paper read at the Quarterly Meeting of the Royal Medico-Psychological Association, London, Nov. 9, 1955.

† This paper and those by Reiss (p. 431) and Robinson et al (p. 439) are also being published in the July, 1956, JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY AND QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY.

and where it is not so, a state of peripheral undersensitivity to thyroid hormone can be detected. This was already suggested by Hoskins and Sleeper when they found schizophrenic patients who were insensitive to enormous amounts of thyroid preparations. The I^{131} tracer method also permits us to differentiate between primary or secondary (pituitary) disturbances.

Similarly, our knowledge of adrenal and gonadal function has been widened by the use of methods for the determination of 17-ketosteroids and corticoids and of chromatographic fractionation of the various ketosteroids. Methods for the determination of the various pituitary anterior lobe hormones are still in their infancy, certainly not yet ready for routine clinical use, but some are already suitable for use in research cases. When the functions of both the thyroid and the adrenal are disturbed, as indicated by the combined results of the tracer and steroid estimations, and when there is a clinically recognizable deviation in body growth or gonads, then it is probable that a disturbed pituitary anterior lobe function exists. A further factor has been that the production of more reliable hormone preparations is progressing.

Last, but perhaps most important, is the fact that the conception of the possible role of endocrines in relation to psychiatry has changed. The original approach to the problem of endocrinological psychiatry was a rather unfortunate one, since the function of certain glands was too much connected with specific psychologic functions. These functions were related too readily to animal experiments. One may cite the loss of fighting spirit of the cock after removal of the testicles and its return after reimplantation of the testicles. We know now that it is by no means always the sex hormone that has a relation to the "fighting spirit," but that the "fighting spirit" depends on a much greater multitude of endocrine and psychologic and genetic factors. We know now that the same hormone can have quite different psychologic action if given to different individuals with varying personality patterns.

Progress has been delayed because we have ignored the common association of mental illness with phases of intense endocrine change at puberty, pregnancy, and the menopause and have continued too long to look for direct causal relationships, in spite of the established fact that diseases of the endocrine glands are not significantly correlated with mental illness, or vice versa. No particular neurosis or psychosis has yet been directly etiologically linked with a particular endocrine disorder. A state of thyroid hyper- or hypofunction is not consistently associated with psychiatric illness, nor are clinically recognizable disorders of the adrenals or gonads or pituitary, though at times all are associated with mental breakdown. We have rather taken the view that, as in puberty, pregnancy, and the menopause, it is the variation in endocrine function that is important, but that, as in these crucial epochs, it is not merely the occurrence of endocrine variation that is significant, but the degree to which that variation differs from a particular individual's normal range, together with the stability of the personality in which these changes occur. Furthermore, it is the personality pattern that will determine the form of the subsequent psychiatric disorder, no matter what the type of endocrine deviation may be. In fact, it is not only the type of hormone that is important, but alteration in its quantity, in so far as this is related to the whole hormone equilibrium.

TABLE I
Thyroid Activity
(Age Group 18 to 21 Years)

	Total no. investigated	No. in normal range	No. below normal range	Per cent below normal range	No. above normal range	Per cent above normal range
Royal Army Medical Corps	78	68	4*	5.1	6†	7.7
Psychiatric patients	131	97	18‡	13.7	16§	12.2

* Lowest 24 hour uptake 20 per cent.
† Highest I_t 12.4.
‡ Lowest 24 hour uptake 4.2 per cent.
§ Highest I_t 18.3.

The number of hormones known to influence the development and function of the nervous system is increasing. Hypothyroidism has been recognized for years as producing arrest of intellectual maturation in the young and as being linked with anxiety in many adults. Cortisone, ACTH, and dehydroisoandrosterone (diandrone) can in certain persons precipitate a psychosis or severe behavior disorder. Conversely, clinical improvement has been reported by Strauss et al in some very immature and socially inadequate schizophrenics and by Sands and Chamberlain in adolescent cases of inadequate personality. Estrogens diminish the quantity of the sexual activity in the male and, in so far as psychoses are concerned, can make an existing psychosis temporarily more acute in certain cases. A similar effect was obtained in some patients treated by chorionic gonadotrophin (Pregnyl). In fact, the whole question of the activation of psychiatric disorders by hormones, including the well recognized activation by insulin, needs further investigation. Obviously hormones can influence the function of the nervous system. The problem is to determine the cases likely to be benefited rather than the reverse.

Robinson assessed the thyroid activity of 110 newly admitted psychiatric patients in the Royal Victoria Hospital, Netley, and also of a parallel series of 78 normal personnel of the Royal Army Medical Corps as controls. The distribution of the thyroid index in this series appeared to follow the pattern of that found by Reiss et al[9] in the psychiatric population of Bristol Mental Hospitals. Psychiatric casual-

TABLE II
Statistical Analysis of Table I

	Within normal range	Without normal range
Royal Army Medical Corps	68	10
Patients	97	34

Incidence of subjects falling within or without the normal range of thyroid index in Royal Army Medical Corps controls and psychiatric patients.
Chi square (d.f. = 1) = 4.318. Significant at $p = 0.05$. (Yates correction applied.)

TABLE III

Iodine Tracer Tests
Since December 1954

	Females	Males
Normal range	67 (55%)	125 (71%)
Above normal	47 (38%)	37 (21%)
Below normal	8 (7%)	15 (8%)

ties between the ages of 18 and 21 years showed a greater number of variations than controls of the same group, as illustrated in table I.

In tables I and II Robinson has shown that the mere occurrence of endocrine abnormality in thyroid function, as measured by the I^{131} uptake in the first hour and after 24 hours, can coexist with ordinary mental health. Conversely, Reiss et al[9] have demonstrated that the majority of mental patients of the average mental hospital population do not show deviations measurable by present methods. In nearly 300 cases investigated at St. Ebba's Hospital during the last year, 65 per cent showed tracer results within normal variation; we also found that females showed results above normal in a significantly greater percentage than males.

Since the cases were in some degree selected, they are not strictly comparable with the series of Reiss et al.[9] None the less, all investigators found endocrine abnormalities, as measured by the same tracer and steroid techniques, in a significantly greater proportion of psychiatric patients than of normal controls. It was these observations that stimulated further inquiry into the possible use of endocrine methods of investigation and treatment, with the expectation that if any definite advance were made it would be on a very limited front. Both psychiatric patients and tracer apparatus are likely to be temperamental, and in order to avoid sources of error the following measurements were made: (1) the I^{131} uptake slope in the first hour; (2) the 24 hour uptake rate by a Ring counter specially designed for psychiatric patients; and (3) the 24 hour and 48 hour urine excretion rates.

Radioactive tracer estimations were performed under the supervision of Dr. W. W. Kay, of the Group Laboratory, making use of the methods employed by Reiss et al[9] and Haigh et al, except that the 24 hour uptake of iodine was checked against the 24 hour excretion rate. If the sum of excretion and uptake was over 100 per cent, the excretion value was preferred. The I^{131} tracer method measures only the rate of iodine uptake, and in order to secure a more adequate view of the activity of the thyroid, a fourth parameter measuring the production rate of thyroid hormone has been added. It is naturally difficult to know just what should be regarded as the normal range of variation, but the controls quoted suggest that we are at least fairly near the truth. The I^{131} uptake in the first hour (K) should be under 3.0, and for the sake of caution the normal 24 hour I^{131} uptake rate was taken as 25 to 50 per cent, instead of the more usual upper level of 40 per cent found in the literature. The normal range of I^{131} excretion was regarded as between 25 and 50 per cent. Ketosteroid excretion measurements were based on the method of Callow and Callow. The normal range in men varies from 9 to 21 mg. and in women from 7 to 15 mg.

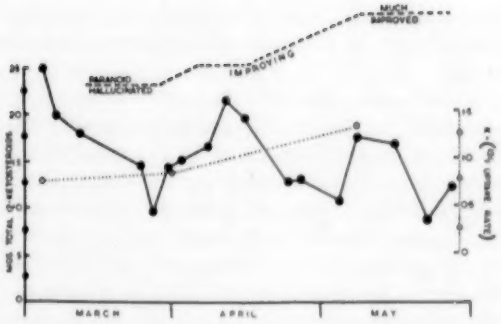

FIG. 1. Graph showing the fluctuation in ketosteroid output often seen in the more acute schizophrenic patient and the decline in these fluctuations associated with improvement in the mental state. Both tracer and ketosteroid results have become more normal as the patient spontaneously progressed.

Experience in general medicine indicates how careful one must be in the interpretation of the significance of biochemical measurements. The normal blood sugar range is from 70 to 120 mg./100 ml., yet diabetics may function for long periods over the upper limit before showing clinical symptoms or signs. Similarly, it is possible to have a serum potassium level below normal a long time before the onset of flaccid paralysis (normal 3.6 to 5.1 M N or 16 to 20 mg./100 ml.). It is evident that normal ranges are not a bar to the onset of symptoms, and abnormal values are certainly no guarantee of the presence of symptoms. We cannot yet speak of endocrine equilibrium in any exact sense, since we can measure only a few of the parameters of certain endocrine glands.

So far we have worked mainly on cases of schizophrenia and psychopathic personality in both adults and juveniles as being types likely to carry a high rate of constitutional abnormality. The majority of patients have been physically examined endocrinologically and have had both tracer and ketosteroid estimations, many with frequent repeating of tests. The main uses of these tests have been in prognosis and treatment.

During routine biochemical examination of the more recent cases, it was noticed that as patients improved clinically, there was also an increasing tendency for the tracer and 17-ketosteroid results to fall within normal ranges, even though the initial tests might not be considered to be more than borderline abnormal. This trend was seen with spontaneous remissions and in patients treated by electroconvulsive therapy, insulin, and amphetamine. An example of this observation is given in figure 1, which shows the fluctuation in ketosteroid output so often seen in the more acute schizophrenic patient and the decline in these fluctuations associated with improvement in the mental state. Both tracer and ketosteroid results have become more normal as the patient spontaneously progressed.

A preliminary report can be given concerning the relationship of steroid and tracer deviations to the prognosis with insulin coma therapy in 17 cases. In each case a tracer test with at least two total ketosteroid estimations, and often more, was done before insulin therapy was started. Independently a clinical prognosis and a prognosis based on the biochemical findings were given for each patient in regard to insulin therapy. The insulin course proceeded in the ordinary way, except that

17-ketosteroid estimations were done on Sunday, the only day on which the patient was completely free from insulin. After treatment, tracer and steroids were repeated. The clinical prognosis was based on the generally accepted criteria, including previous personality, duration of illness, mode of onset, maintenance of affect, and so forth. The biochemical prognosis was based on: (1) The clinical assessment of physical development and in particular of the gonads. Only macroscopically severe degrees of abnormality were considered. (2) The 17-ketosteroid excretion rate, an increased excretion rate indicating increased adrenal function, and vice versa. (3) Thyroid activity, as measured by tracer and basal metabolic rate.

The outcome of the investigation was that, of the 17 patients, the clinical and biochemical prognoses substantially agreed and were correct in 10 patients. In 4 the clinical prognosis proved wrong and the biochemical right, and in 3 the clinical prognosis was correct but the biochemical wrong. For what it is worth in this small group, the biochemists are so far one up on the clinicians.

In general, it was evident that where 17-ketosteroid excretion was high and the thyroid tracer result low or average, the prognosis for insulin therapy was satisfactory. High thyroid tracer and low 17-ketosteroid excretion, or low results in both tests, were associated with poor insulin therapy results. Although some patients showed an initial rise of ketosteroid output, in the more successful patients ketosteroid levels tended to fall sometimes below normal range during the course, though the original level might be nearly regained after treatment. The success of insulin therapy in those patients having a high 17-ketosteroid excretion rate at onset seems consistent with the improvement gained by Broster after adrenalectomy in psychiatric patients with hyperadrenalism and with the temporary psychotic disorders seen after increased ACTH and cortisone administration. Altschule and others have put forward the view that success with insulin therapy is due to some degree of exhaustion of the adrenals. Our own small experience would tend to support this view. Equally, if the ketosteroid excretion is already low before treatment, it may be inadvisable to lower it further. The presence of physical immaturity, both in the body generally and in sexual development, was also associated with poorer results. If substantiated by the further work now proceeding, these last two observations would be consistent with my observation that in juvenile and adolescent schizophrenia it is unusual to obtain a good insulin coma result until after the age of 15 or 16 years, when the adrenarche is nearly complete and when the 17-ketosteroids are approaching adult levels. These remarks apply mainly to the more recent cases of schizophrenia and to results after treatment without follow-up.

Since it is clear that a number of different hormones can influence the function of the nervous system, it was thought advisable to concentrate mainly on discovering what their limitations and possibilities might be before giving full attention to any role they might possess in therapy. For this purpose, selected patients were given a physical endocrinological examination, tracer and 17-ketosteroids also being estimated when the patients were not on other forms of treatment. If the examinations were all negative and endocrine equilibrium was undisturbed, no further steps were taken except sometimes to repeat these tests, particularly if spontaneous remission was likely. If illness continued, an attempt was made to modify the function of the

particular endocrine gland or glands that appeared to be abnormal by reason of the tests made, and then to correlate subsequent biochemical changes, if any, with the progress of the mental state.

The techniques employed are probably best illustrated by actual cases. For instance, a man of 29 years was admitted with a provisional diagnosis of schizophrenia, with gross thought blocking, stilted behavior, and obvious inadequacy both in affect and in social responses. He had been discharged from the Army in 1944 with a diagnosis of inadequate personality, and in another hospital to which he was later admitted he was labeled schizophrenic. His background showed domination by his mother from early life, few friends, a quiet, rather withdrawn attitude, no interest in girls, and a general history of social inadequacy. He was clearly not a suitable candidate for insulin therapy, and he failed to respond to psychotherapeutic and rehabilitative measures. Because of his clinical inadequacy, and since his ketosteroid output in two specimens was at the accepted lowest normal level and the beta percentage was also low, he was given 20 mg. of diandrone daily. Strauss et al and Sands and Chamberlain have previously reported a good therapeutic response in similar patients. Over a space of three months the dose was raised to 60 mg., but there was only a very moderate mental response; the patient was more cheerful, but was still slow and inhibited. A few months later tracer results showed that thyroid iodine uptake was too low, but 17-ketosteroids were within the upper normal range. He was given thyroid extract, 1 gr. daily, the dosage being finally raised to 4 gr. The staff reported improvement in his slowness, conversation, and sociability after six weeks. This has been confirmed by his doctor, and the improvement has been maintained over the last seven months on 2 gr. of thyroid daily. It will be noted that first diandrone was given unsuccessfully on the basis of clinical and steroid findings only, but there is no doubt in the minds of those who have his daily care that the patient's mental improvement has resulted from the administration of thyroid. The schizophrenic aspects of his condition had already improved after his admission to the hospital, and the main difference after thyroid has been in the features that formerly made up his very schizoid, socially inadequate personality.

Patient L., 18 years of age, was referred from the Assize after assault and stealing. His father was aggressive and dominating, but his mother was self-effacing and a poor mixer, the pattern mainly inherited by the patient, who was sent away to boarding school when 6 years old. The patient described himself as seized by tension when frustrated, followed by a fantasy of seeing himself in a uniform, usually of a post-office messenger boy or a boy scout. He obtains the uniform by stealing or assault, dresses himself in it, experiences full sexual stimulation on looking at himself in a mirror, and then relief of his tension. He was treated psychotherapeutically for 13 months, but continued to be unsettled and was agitated and restless at times; during this period he stole a bicycle. I^{131} tracer tests indicated thyroid underfunction (E_{24} 64 per cent, E_{48} 67 per cent, K 0.85); serum cholesterol was 98 mg./100 ml. 17-Ketosteroids were in the upper normal range. Although he had been used to having other drugs and tablets, he improved on 2 gr. of thyroid daily, now being more confident, a better mixer, and able to sleep without sedatives. In

the morning he was depressed for a time, but he has now lost this feeling and all interest in uniforms. Temporary reduction of the thyroid over 16 days resulted in some relapse, particularly in regard to homosexual thinking. Since the dose has been restored he has improved, his ideation is predominantly heterosexual, and he makes a more masculine impression. He will probably need thyroid indefinitely.

A different approach was used in a boy of 13 years, who was referred with a two and a half years' history of increasing nervousness and irritability, with laughing, gesticulating, and a habit of talking to himself. The parental management had been very ill balanced. His birth had been a difficult one, and physically he showed much pubic hirsutism and undescended testes. When he was seen, his talk wandered inconsequentially and he had various mannerisms and seemed "odd" in a superficially adult way. He made no friends in the ward and was merely tolerated by the other boys and pushed around by them. His iodine tracer result was normal, but 17-ketosteroids were uneven and at times high. The fractionation of ketosteroids showed that dehydroisoandrosterone was increased, while androsterone was decreased. An attempt was made to normalize the ketosteroid metabolism by the use of chorionic gonadotrophin (Pregnyl), 1500 units daily intramuscularly, with the result shown in figure 2. Psychologically the patient appeared to show more initiative, to be able to stand up for himself, and to be mixing better socially. This change has been maintained for the last four months, and he has been discharged.

Concerning testicular hormone, its applications would appear to be three: (1) in small doses for the stimulation of pituitary function; (2) in somatic immaturity with adrenal and testicular underfunction; and (3) as an anabolic stimulant where weight loss is severe in cases of hysterical and pituitary anorexia.

In the first category the following patient showed some benefit from the use of depot testosterone. A boy of 12 years, small in stature, shy by disposition, much indulged by his mother, was admitted to the juvenile department because of temper tantrums, truancy with refusal to attend school, complaint of pain in the stomach, and a feeling of suffocation and a lump in his throat. He was much teased at school. He had been very preoccupied with his health and was indifferent to sports, preferring solitary occupations. He was regarded as being in an anxiety state with physical and social immaturity. He adjusted to the hospital fairly well and somatic symptoms diminished, but he attacked his mother at visiting time. In view of his continuing instability he was investigated further. Intelligence proved average; the electroencephalographic record showed immaturity; genital and pubic hair development was backward; both thyroid tracer test and 17-ketosteroid output was low, suggesting pituitary underfunction. He was given Primoteston (a depot form of testosterone), 250 mg. weekly. About a week after the first injection he stated that he felt better, that he could run about more, and that he noticed he did *not* lose his temper, even when teased by others in the juvenile ward. Physically, he gained 11 lb. in two weeks and 1 inch in height during his stay; pubic hair began to grow and his penis and testicles increased in size. The school reported improvement in educational performance, his arithmetic results in the Southend test moving from 8 years, 5 months to 10 years, 7 months. The tracer level and ketosteroid output increased from low to average levels. He was discharged home recovered after 11

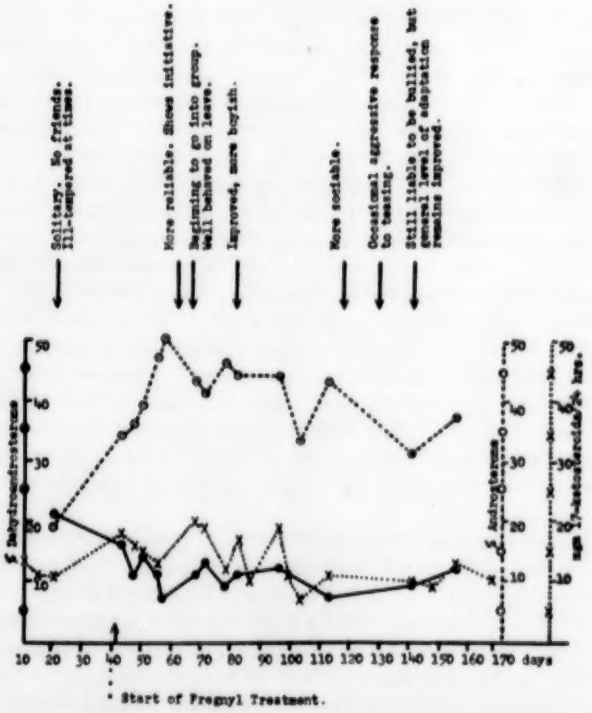
Solitary. No friends. Ill-tempered at times.
More reliable. Shows initiative.
Beginning to go into group. Well behaved on leave.
Improved, more boyish.
More sociable.
Occasional aggressive response to teasing.
Still liable to be bullied, but general level of adaptation remains improved.
mg. Androsterone
mg. Testosterone
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 days
Start of Pregnyl Treatment.

FIG. 2. Graph showing results of an attempt made to normalize the ketosteroid metabolism in one patient by the use of chorionic gonadotrophin (Pregnyl), 1500 units daily intramuscularly. Psychologically the patient appeared to show more initiative, to be able to stand up for himself, and to be mixing better socially.

weeks in the hospital. It is felt that admission to the hospital and psychotherapy improved the anxiety symptoms, but the patient remained constitutionally immature and liable to relapse. His responses to stresses subsequent to five injections of Primoteston depot were greatly improved, and no further aggressive episodes occurred.

The following patient, a boy of 13 years with somatic immaturity and testicular and adrenal underfunction, may be considered as falling into the second group. He was chronically anxious and inadequate. In disposition he was shy, sensitive, and apt to be jealous of his siblings. He had stammered from 2½ years of age, was a chronic nail biter, and for a year avoided school by complaint of aches and ailments or truancy. Physically, secondary sex characters were absent, the penis was very small, and the testes liable to return back into the abdomen when the boy was lying down. Ketosteroid output was low (3.2 and 3.8 mg./24 hours), but the tracer result was in the normal range. The electroencephalogram was mildly abnormal,

with marked instability on overbreathing. After five weeks of routine treatment with psychotherapy, education, and occupation, the patient was fairly settled in relation to the other boys, but he still stammered. He was given Primoteston, 50 mg. every three weeks, with some improvement in his stammering, but he became rather defiant and bullying. After two and a half months the Primoteston was doubled and given biweekly with diandrone, 10 mg. twice daily, because the ketosteroid output had remained low and the stammer relapsed. This resulted in a gain in the quantity but deterioration in the quality of his language, and he could certainly swear without stammering. At this stage the 17-ketosteroid excretion rate had reached a plateau of 9 mg./24 hours. He became so rebellious, irritable, and aggressive, especially three days after the injections, that it was plain that he had been overdosed with testosterone, and he was taken off it, but diandrone was continued. On this regime he settled down and volunteered the observation that diandrone "made me not bother about my stammering so much." He gained 2 stones in weight in four months, his school performance improved, and he was discharged home much improved. This case indicates the effects of excessive testosterone medication mentally, even though the patient matured physically, whereas diandrone proved the more successful from the psychiatric angle, improving stammer and social performance.

In regard to the third indication, anabolic effects have already been obvious, but in anorexia nervosa there may be a special field for its use. A girl of 14 years was referred because of severe anorexia present since 1951. She was emaciated, had lost 3 stones in weight, and had the elderly look of the chronically starved. She was very unstable and immature emotionally, was childish, and at first just pecked at her food. The mother was tense and full of guilt and gave in to the daughter's every whim. The patient's hands were slightly cyanotic, her breasts were barely developed at all, and although much downy hair was present on the face, pubic hair was negligible. The thyroid tracer result was in the normal range (E_{48} 44.1 per cent, K 1.35, I_1 3.06), but 17-ketosteroid excretion, at 3.7 and 3.0, suggested underfunction of the adrenals. Under chlorpromazine, 25 mg. three times daily, she was persuaded to start eating a little. She gained little weight on chlorpromazine, although emotionally she improved. After four weeks she was given Primoteston depot, 50 mg. intramuscularly weekly. She gained 4 stones in the next three months, moving from 4 st., 4 lb. on admission to 8 st., 5 lb. on discharge (fig. 3). She had an excellent appetite, regained her color, and lost the hair on her face, but developed pubic and axillary hair. She became lively and cheerful, and looked her age. The likelihood is that chlorpromazine enabled her to take some food, so that the anabolic action of testosterone could take effect and eventually create more of an appetite. 17-Ketosteroids rose to 6.7 mg. (in the normal range for this age).

By way of a tailpiece to the use of testosterone, I might mention the 30 year old married man who, having suffered from psychogenic impotence and fetishism for 18 months, was relieved in the course of three weeks by testosterone, 50 mg., and diandrone, 10 mg., both intramuscularly daily, eventually achieving normal sex relations with his wife four times in 24 hours.

There are times when the reverse situation occurs. It may be necessary to control

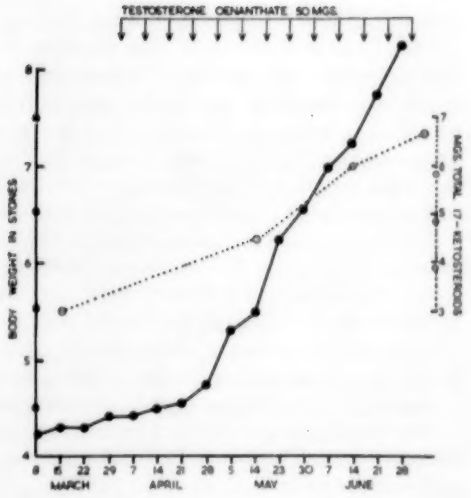

FIG. 3. Graph showing weight gain in one patient given Primoteston depot, 50 mg. intramuscularly weekly.

actual or relative precocity, as illustrated by a 14 year old boy admitted on probation after indecent assault of a 10 year old girl, and who, a month previously, had had homosexual behavior with another boy. In his home, which was otherwise satisfactory, the subject of sex was completely taboo, and he was quite uninstructed in it except through school acquaintances of the wrong type. In consequence he felt handicapped in associating with schoolmates on equal terms. Contrarily, he felt that undressing in front of other boys was embarrassing, though he had exposed himself to others in his offenses. Physically, his genitals and pubic hair were most precociously developed, and he masturbated three to four times a week. In view of his history, and because of the disparity between his physical and his psychologic sexual development, he was started on stilbestrol, 1 mg. daily orally, which was increased by 1 mg. weekly to 4 mg. After two weeks he said his sexual urges were diminishing: "I feel I am able to control myself," and again: "I do not feel filthy now." He masturbated only once in two and a half weeks, and began to be less shy about undressing. Psychotherapeutic discussions were productive; after five weeks, reduction of stilbestrol was gradually effected and it was omitted after seven weeks without relapse. Estimations of thyroid activity by tracer tests and of 17-ketosteroid excretion were normal before treatment was started, though 17-ketosteroids were subsequently depressed by stilbestrol. The thyroid tracer results remained in the normal range. The boy may need further occasional short courses of estrogens until balance is achieved between physical and psychosexual maturity. He departed much improved, to return home and to his school.

The patients discussed have been generally assisted by treatment, and the results of biochemical investigations have shown some value in prognosis. There is another side. A 15 year old girl was admitted from another hospital, having developed a schizophrenic illness during cortisone therapy for acute articular rheumatism and

carditis. First depressed, she then became confused and restless and talked of being in heaven and hearing angels. She displayed mannerisms, rocked to and fro, smiled incongruously, talked nonsense, used neologisms, and was incontinent. She began to improve after three weeks, and eventually emerged as a shy, quiet type of girl who had no further difficulty. When her psychiatric disorder settled, there was some correlated physical improvement, though exercise tolerance continued to be low. She returned to the original hospital and has since been given a post on the staff within her physical capacity. No previous mental instability was known.

A borderline defective girl of 15 years had had a schizophrenic attack with some hysterical traits. She had also been reported to have what were described as periods of silent withdrawal for about a week since the menarche, which was at 12 years. In the hospital, phases of apathy and poor cooperation appeared to be associated with her menstruation. During her stay she was given diandrone, 10 mg. daily orally, because of inertia, slowness, and lack of initiative, but after two days she became noisy, overactive, aggressive, and abusive, to the extent that transfer to another ward was necessary. The reaction subsided after five days, and thereafter the patient settled down and her behavior was consistently good. 17-Ketosteroids were low for her age.

Both these last patients broke down into short psychotic illnesses when given adrenal steroids in adolescence, though the dosage was quite average. Both were immature in different ways, and appear to have been unable to adapt to a further increase of adrenal steroids above that which normally takes place in adolescence.

The response of chronic cases needs further investigation, but it is already evident that many such patients become highly resistant to endocrine administration, and the situation is the opposite of the patients just mentioned. A youngster of 13 years, a boy with a history of schizophrenia since early childhood, having a somewhat immature physical sexual development, normal thyroid and basal metabolic rate results, but fluctuating 17-ketosteroid output, was given 50 to 150 mg. of testosterone depot injections over seven months without any mental reaction at all, though physical maturation improved. It was noticed that this boy had a considerable capacity for disposing of testosterone, since injections of 150 mg. depot did not

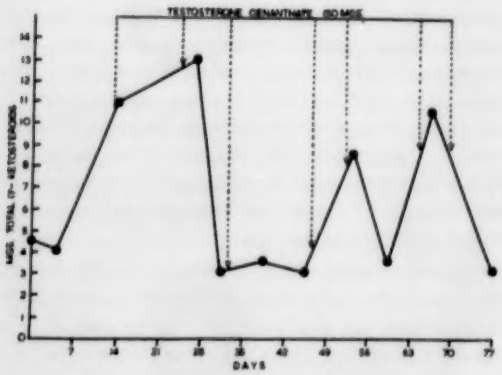

FIG. 4. Graph showing considerable capacity of one patient for disposing of testosterone. Injections of 150 mg. depot did not appear to raise the 17-ketosteroid output for more than six days, though other patients showed a rise for 16 days or more.

appear to raise the 17-ketosteroid output for more than six days, though other patients showed a rise for 16 days or more (fig. 4).

Another 15 year old boy with a four year history of schizophrenia that had defied all forms of therapy, including a standard leukotomy, was given 1000 mg. of testosterone in depot form, guarded with 20 mg. of stilbestrol, daily for 10 days. Clinically, he was quite unmoved for better or worse by this large experimental dose. His 17-ketosteroid output, which usually fluctuated from 6 to 11 mg., moved to 21 mg. the day after injection, was 17.6 after a week, and three days later was only 4.5 mg., no doubt under the continuing suppressive influence of stilbestrol.

COMMENT

Certain observations can be made from the work done so far. Regarding the incidence of normal and abnormal thyroid and steroid estimations, the reports of Reiss et al[8, 9] at Bristol have been largely confirmed, as has also their observation that normal findings in a recent case are usually of good prognosis, and that in chronic patients the thyroid and adrenal functions have again become stabilized within normal limits. Concerning insulin coma therapy, it is well known that for a number of years the diagnosis of early schizophrenia of less than two years' history has been practically synonymous with the administration of insulin coma, with a fair degree of success. However, not all recent cases respond to insulin, and obviously much time, effort, money, and inconvenience would be saved to all concerned if it were possible to be more selective. Insulin coma therapy itself is an undoubted stress, and in the small group of patients investigated there were some who before treatment did not show the usual evidence of increased adrenal cortical function with raised ketosteroid output. Such patients may also show immaturity in primary and secondary sexual development. These patients were always associated with an early history of considerable stress in childhood and early adolescence, and it would appear that their reactions to stress were either inadequately developed or exhausted. Those who are familiar with the more drastic methods of physical treatment know that some recent schizophrenic patients seem unaltered by electroconvulsive therapy, insulin comas, or leukotomy, and they come to be thought of in terms of dementia praecox rather than of schizophrenia. At present I can only say that they are very like the failures in the present small series. By contrast, patients showing signs of raised adrenal cortical function, with normal or even depressed thyroid activity, did well. In normal persons ketosteroid output varies little, but in active cases of schizophrenia there is often much fluctuation.

Twenty to 25 patients have been given androgens, either by daily injections of testosterone or by less frequent use of androgen depot preparations. Both testosterone and diandrone are now available in depot form. The duration of their effect is not as long as has been claimed and in some cases may be less than a week, even with fairly high dosage. In most patients the effect will not last longer than 16 days and should be correlated with weekly ketosteroid estimations until the duration is more accurately known. None the less, for prolonged androgenic action such preparations are an improvement.

Clinically, testosterone has improved these adolescent patients who were emotionally, socially, physically, and biochemically immature, who have felt inferior, become anxious, and shown behavior disorder on this basis. Even if occasional tempers have been shown in the past, testosterone does not worsen such aggression so long as the patient is basically inadequately immature, though individual regulation of dosage is needed, since overdosage can swing even these patients into an irritable, aggressive phase. In the immature adolescent it has not provoked any strong overt signs of sexual activity. In older patients it can stimulate much sexual thinking and fantasy, in addition to a sense of greater energy and mild euphoria. Homosexuals cannot be changed to a more masculine attitude. In most of them, testosterone merely accentuates the homosexuality. In general, its action is to increase the quantity of the sex drive without in any way altering its main direction. There are patients who have both homo- and heterosexual qualities, and in those in whom the heterosexual activity is predominant it can help maturation, particularly if environment is also suitably adjusted.

The adrenal androgen, dehydroisoandrosterone (diandrone), has an action similar to that of testosterone in promoting increased confidence, activity, and at times aggression, but it seems to have little stimulating action on physical maturation of sex organs and characters or an effect on sexual fantasies, or any anabolic effect. It can provoke aggression and is clinically indicated when the immaturity is limited to social and emotional fields, such as was described in previous reports. We know from papers by Widdowson and others that chronic stress can impair physical and mental development in childhood. It is in persons of this type, who have subsequently broken down in adolescence and early adult life, often under quite ordinary strains, that androgens have a sphere of usefulness in raising the threshold of resistance to stress. I have seen such youngsters "grow up" both physically and mentally under the single or combined use of these androgens.

When gonadal and psychosexual development is precocious, leading to overactivity, tempers, undue masturbation, sexual assaults, and homosexuality, it may be necessary to depress sex drive and delay further sex maturation until the patient is more mature in other ways. Stilbestrol and Dimenformon have both proved effective and, when linked with psychotherapy and social supporting measures, have kept the immature and the psychopathic person out of further trouble.

Although some reference has been made to hormonal influences of therapeutic value, the first requirement is to discover more about their relationship to the nervous system and about their own normal variation and to improve biochemical measurements. From the present series of patients tested, one can say that present biochemical methods are of value, particularly if frequent repetition and long term studies are possible. There is still too much wastage, partly because of imperfections of technique and partly because these methods, originally developed for use in general medicine, need further modification before they can be fully applied to psychiatric patients. It is probable that it will be necessary to arrange for tracer tests to be done under similar conditions to the basal metabolic rate, or with the use of sleep, to exclude factors at present causing occasional inaccuracy. Even now, when combined with clinical assessment, these methods can in some cases give

information of prognostic value or indicate a line of treatment that might have been missed on clinical psychiatric grounds alone. For the most part, hormonal action is linked with major factors in maturation and constitutional function, e.g., growth, reproduction, nutrition, and the homeostatic mechanisms of the nervous system. There is no evidence as yet that hormone action has much part to play in the symptomatic treatment of any of the common syndromes of psychiatry per se. Indeed, hormones may aggravate a neurotic or psychotic reaction by further disorganizing the individual's endocrine requirements, so that hormone imbalance becomes a stress in itself. The cases we have studied suggest that the role of hormones in relation to disorders of the nervous system is not so much in bringing symptom relief as in the correction of the chronic deviations of personality development that underlie so many psychiatric disorders. These come to light when physical methods clear up the more acute manifestations, or during the process of psychotherapeutic investigation, and one is left with what is sometimes described as a "vulnerable" personality, labeled perhaps as predominantly schizoid, depressive, obsessive, or psychopathic. These personality deviations are the joint result of heredity and earlier stresses, even from childhood. At puberty they are usually still in a developing and modifiable stage, and the sample patients discussed suggest that investigation and treatment at this stage may be the most rewarding.

Endocrinology and psychiatry both suffer a history steeped in controversy, with flashes of success and many failures. On the evidence available, there is nothing at this stage to warrant the deduction of firm conclusions on the relationship of endocrines to psychiatric disorder, but one only begins to see some indication of what the endocrine role will be. The standard approach of clinical and biochemical correlation, succeeded by such therapeutic intervention as has seemed indicated, has been reported here. There is no indication that the endocrine method will ever be a complete treatment for any psychiatric disorder, but by attention to this hitherto rather obscure field we may be able to improve considerably our patients' ability to adjust to stress, and to supplement usefully our efforts to do precisely the same thing from psychotherapeutic angles. In short, endocrinology may be able to increase the patient's potentiality for normal adaptation, but it will continue to be necessary for the psychiatrist to show him how to use it.

SUMMARY

A reassessment has been made of the function of the endocrine system in relation to various psychiatric states. Investigations have been performed, chiefly on the adrenal and thyroid activity of over 300 juvenile and adult psychiatric patients. A preliminary report has been given concerning the relationship of steroid and tracer deviations to the prognosis of insulin coma-treated patients. Selected cases are described, illustrating the influence of different hormones on the nervous system. Some tentative conclusions have been drawn on the possible role of endocrines in therapeutics.

ACKNOWLEDGMENT

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New Pavilion of Saint Elizabeths Hospital Formally Dedicated

The new $6 million Dorothea Lynde Dix Pavilion of Saint Elizabeths Hospital, Washington, D. C., was formally opened on April 13 with dedication ceremonies featuring an address by Vice President Nixon. Marion B. Folsom, Secretary of Health, Education, and Welfare, of which Saint Elizabeths is a component, describes the new facilities as "a symbol of progress in the psychiatric world generally, and as providing for a major advancement in the care and treatment of the mentally ill, in which Saint Elizabeths has been the leader since its beginnings in 1855."

The 10 story building, for which ground was broken Feb. 1, 1953, is named for Dorothea Lynde Dix as a memorial to her tremendous contribution to professional and public understanding of the need for humane care and enlightened treatment of the mentally ill.

The new Pavilion provides for 420 beds with one-, two-, or four-patient rooms and will operate as a receiving and intensive treatment center with therapeutic and rehabilitative facilities and personnel. The physical planning by architects and psychiatrists provides for a homelike community atmosphere.

Dr. Winfred Overholser, Superintendent of Saint Elizabeths and Editor of the Quarterly Review of Psychiatry and Neurology, sees the new building as "an important new step in carrying out the principles that have guided the work of Saint Elizabeths for a century; one that will assist us materially in breaking down the psychological wall between the hospital and the community."

Endocrine Concomitants of Certain Physical Psychiatric Treatments*

M. Reiss, M.D., D.Sc.

DIRECTOR, BIOCHEMICAL AND ENDOCRINOLOGICAL RESEARCH UNIT
BARROW HOSPITAL, BARROW GURNEY, NR. BRISTOL, ENGLAND;
HON. CONSULTANT TO ST. EBBA'S HOSPITAL, EPSOM, AND
ROYAL VICTORIA HOSPITAL, NETLEY, ENGLAND

When studying endocrinological psychiatry one finds that contrary to previous conceptions that have always tried to connect hormone action with various psychiatric syndromes, there is no specific correlation between any particular endocrine disease and any special psychiatric disorder, and, conversely, mental disturbances can be accompanied by a multitude of endocrine deviations.

The great majority of clinically recognizable and intermediate endocrine disturbances have no primary bearing on the development of mental disease. However, when the individual is subjected to various precipitating stress conditions and has to become adjusted to them, it is then that the role of the endocrine is decisive. Such adjustment is possible only as long as the endocrine equilibrium is in a state to guarantee a sufficient width of adaptation. In many instances, however, the precipitating factors can bring the endocrine equilibrium into disorder, either directly or via the resulting mental stress. The outcome of such a situation can consist of various disturbances in the somatic function and can also be an important link in the physiopathology of mental breakdown. When reviewing the whole field one realizes that a great number of quite different stress conditions can precipitate various psychiatric disturbances, according to the personality pattern of the individual, which are accompanied by endocrine deviations that often can be analyzed by our still rather primitive methods of endocrine analysis. The present scope of psychoendocrinology has recently been reviewed by the author.[1]

It is interesting that a great number of treatment procedures in psychiatry consist in the application of more or less standardized severe stress conditions. When comparing the multitude of the possible precipitating stress conditions with the stresses applied therapeutically, one may best liken the situation to the casting out of devils by Beelzebub.

When studying the development of mental breakdown and disease and some of the treatment procedures, it is interesting to investigate the endocrinological concomitants. This is already being studied by us with the help of the few reliable methods that are at our disposal in clinical endocrinology. In order, however, to get an idea about the principal directions in which certain applied stress conditions influence the endocrine system, we have to resort to animal experiments.

Investigations on animals can give us some idea of the complexity of the various changes in the endocrine equilibrium that occur during and after stress. However,

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* Based on a paper read at the Quarterly Meeting of the Royal Medico-Psychological Association, London, Nov. 9, 1955.

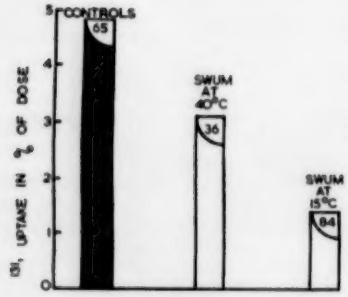

FIG. 1. I^{131} uptake by thyroids of male rats after swimming for 15 minutes.

we have to be extremely careful when making deductions from such experiments about endocrine changes produced on patients under stress conditions or physical treatment. Investigations on animals are always carried out on an object in which the initial condition of the endocrines is well circumscribed and in a situation where plenty of controls are available and statistical evaluation can be done on the basis of unbiased samples. Similar statistical evaluations on human beings are only too often valueless since the authors do not realize that their samples are biased and that, for example, the same stress condition will have an entirely different effect on someone whose adrenals or thyroid is not working sufficiently. I would go so far as to

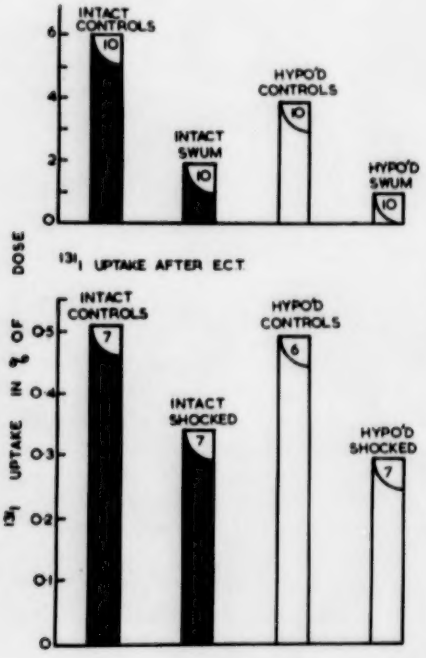

FIG. 2. I^{131} uptake by thyroids of intact and hypophysectomized male rats after swimming at 15 C. and after electroconvulsive therapy.

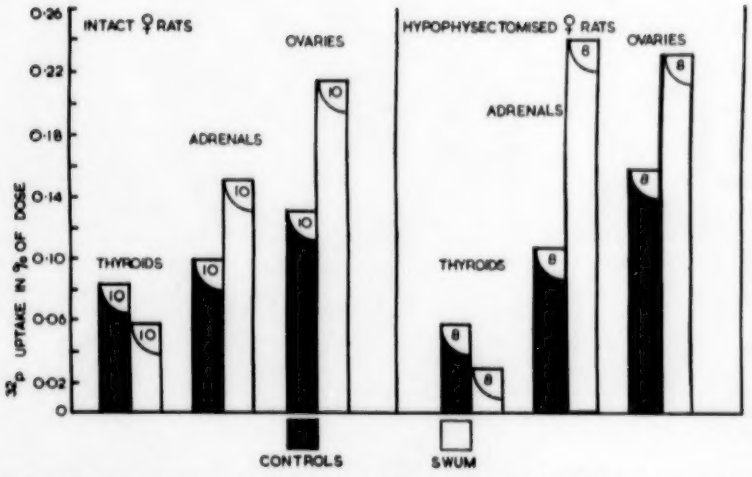

FIG. 3. P^{32} uptake by various glands of intact and hypophysectomized female rats after swimming in water at 15 C. for 15 minutes.

say that it is completely impossible to reproduce in an investigation on any animal exactly the manifold variations possible in the human hormone equilibrium. Only long term investigations on individual patients can bring us any further. The results of animal experiments point only to some basic laws in the endocrine regulatory mechanism and show the direction in which changes in the human organism might be expected under certain conditions.

Inspired by the observation of various endocrine changes and reactions seen in patients, my co-workers (Brimblecombe, Badrick, J. Reiss, Wyatt, and Redman) and I have been trying for several years to understand more about the changes that occur in the hormone equilibrium after various stress conditions.

Contrary to the general belief that all the acute changes found after stress are mediated by the pituitary, and particularly the pituitary adrenal cortex axis, it appears from our own investigations that in fact, many acute stress reactions are independent of the pituitary; also they are not solely restricted to the adrenal cortex. For instance, figure 1 shows that swimming in cold water for 15 minutes reduces the thyroid activity, as expressed by the I^{131} uptake, by about 70 per cent, whereas less stress, such as swimming in warm water, reduces the I^{131} uptake by only about 30 per cent. Figure 2 illustrates that the thyroids of hypophysectomized rats show similar changes after swimming. One can also see in figure 2 that the thyroid activity is reduced 30 minutes after a single electroshock treatment and that there is no difference in this direction between the reaction of intact and hypophysectomized animals.

However, after acute stress there is considerable change not only in thyroid activity, but also in the activity of the adrenals and, to a certain extent, of the ovaries. Figure 3 shows that the P^{32} uptake rate of the thyroid is considerably decreased

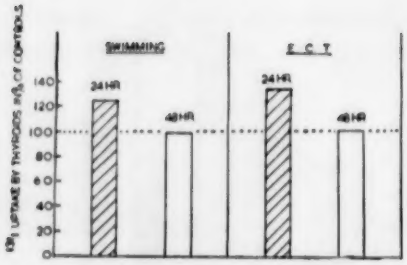

FIG. 4. I^{131} uptake by thyroids of male rats 24 and 48 hours after swimming or electroconvulsive therapy.

after swimming in cold water, while the P^{32} uptake rates of the adrenal and ovary are significantly increased, but identical changes also occur in animals previously deprived of the pituitary. Supported by some further results after adrenalin treatment of animals, we reached the conclusion that the acute stress effect on the hormone equilibrium is to a considerable part due to the mobilization of vasoconstrictor substances.[2]

It seems that the action of the pituitary anterior lobe after stress is more in the manner of a regulating response of the lobe to the changes occurring under acute stress. For instance, 24 hours after swimming or after electroshock, the I^{131} uptake of the thyroid is significantly increased (fig. 4).

It was most interesting, in this connection, to investigate the hormone content of the pituitary. We investigated the pituitaries of stressed animals for their ACTH content by the ascorbic acid depletion method. The thyrotrophic hormone content of the pituitary was investigated by the method recently worked out by Reiss and Wyatt[3] based on the I^{131} uptake by the thyroid of newborn animals.

Figure 5 shows how the ACTH content of the pituitary is continuously kept down by daily electroshock treatment, and figure 6 shows that in the same pituitaries in which the ACTH content is decreased, after a single electroconvulsive therapy treatment the thyrotrophic hormone content is significantly increased.

The action of insulin coma on the ACTH content of the rat pituitary seems to be

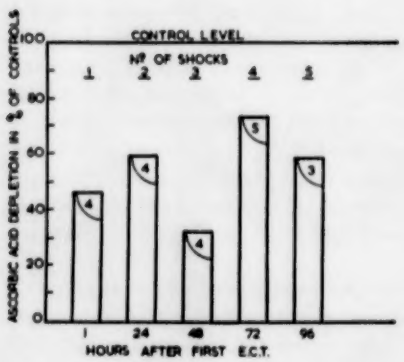

FIG. 5. The effect of repeated electroconvulsive therapy on ACTH content of fresh rat pituitaries.

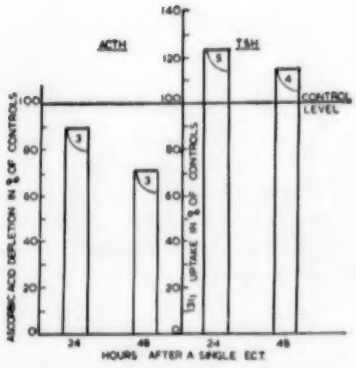

FIG. 6. The effect of electroconvulsive therapy on the ACTH and thyrotrophic hormone content of fresh rat pituitaries.

quite different. After one single coma the ACTH content was found to be increased for the first three days and decreased from the fourth day onward (fig. 7). However, the insulin action on the pituitary endocrinology and the endocrine function of the pituitary is variable and very involved; it is at present still the subject of our intensive investigations.

After investigating the effect of such stress conditions on some endocrine functions, it was of some interest to investigate the action of a drug that is supposed to protect against stress, chlorpromazine. We were rather surprised to find to what considerable degree this drug influences the hormone equilibrium. After four days' treatment with chlorpromazine, the thyroid weight was decreased, but its I^{131} uptake rate was significantly increased, while the adrenal cortex weight was increased and the ovary weight considerably decreased; also, thyroid function was reduced, as was concluded from the lower uterus weight (table I).

Investigation of the pituitary anterior lobe of animals treated with one injection of chlorpromazine revealed a considerable increase of the ACTH content (fig. 8).

If one considers how manifold are the various causes for the disturbance of the adaptation width and of the hormone equilibrium of a mental patient, it will be realized how very much a gamble some of the treatment procedures are. The same stress condition can repair in one case and aggravate in another some disturbances of the hormone equilibrium.

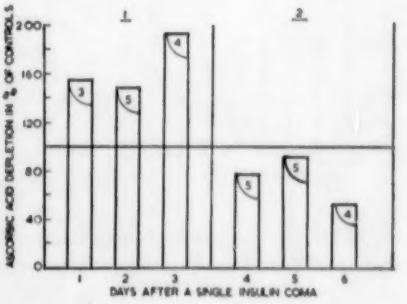

FIG. 7. The effect of insulin coma on the ACTH content of fresh rat pituitaries. Comparison of two experiments.

TABLE I

Influence of Chlorpromazine on Hormone Equilibrium

Treatment	No. of rats	Change in body wt. (Gm.)	Wt. of thyroids		I^{131} uptake by thyroids in % of dose (18 hr.)		Wt. of adrenals		Wt. of ovaries		Wt. of uterus		Wt. of pituitary	
			*	†	*	†	*	†	*	†	*	†	*	†
Controls	8	+4	13.2±2.6		21.1±3.3		59.3±8.9		61.4±9.7		327±103		10.6±1.5	
Chlorpromazine, 6 mg. 2 times daily for 5 days	7	−18	10.6±2.0	−20‡	29.6±7.6	+40‡	75.5±10.7	+27§	41.8±12.3	−32§	249±66	−24	10.3±1.8	−3

* Mean±standard deviation (mg.).
† Per cent change from controls.
‡ Denotes significant change at $p = 0.05$.
§ Denotes significant change at $p = 0.01$.

The main purpose of psychoendocrine research will have been achieved once the endocrine changes accompanying spontaneous improvement or improvement after various treatment procedures have been exhaustively elucidated. Only then could one try to imitate either the working of the body's own regulatory mechanism or the changes produced at present by dramatic therapeutic methods. A modest beginning has been made in this direction.

However, one has to bear in mind that even if it should be possible one day to improve acute psychiatric conditions by rational hormone therapy, it would not necessarily mean that such an approach would be able to influence chronic conditions any more satisfactorily than is possible with the most dramatic treatment procedures used at present. When a pathologic thought content has become fixed in the brain, even a completely normal hormone equilibrium—and we have seen repeatedly that the latter can normalize itself spontaneously in the course of years—has very little influence on the psychopathologic phenomenology. However, one never knows whether we will not be able one day to penetrate the protective mechanisms that make possible the fixation of pathologic thought content. This is

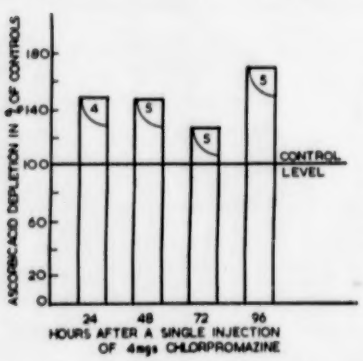

FIG. 8. The effect of chlorpromazine on ACTH content of fresh rat pituitaries.

obviously also a mechanism, the functioning of which is the basic condition for the ability of the brain to learn and accumulate experience.

The question is whether such a mechanism might be connected to some extent with the blood brain barrier. We have lately found some interesting facts concerning the role of the blood brain barrier in the action of thyroid hormones on the brain metabolism of adult rats and rabbits. We have investigated for many years the action of thyroid hormone on the brain metabolism, but have been unable to demonstrate an increase in the brain oxygen consumption, even after treatment for seven days with high doses of thyroxin or thyrotrophic hormone at a time when the oxygen consumption of the liver and of the other organs was very considerably increased.

We then tried to investigate the action of thyroid hormone on the brain oxygen consumption of newborn rats and to our surprise found that in these animals, a significant increase in the oxygen consumption of the brain was regularly produced by thyroxin, triiodothyronin, and thyrotrophic hormone.[4] It was assumed that the brain blood barrier of these animals is not yet properly developed, and therefore the oxygen consumption of the brain can be raised. In further experiments we tried to see whether it is possible to break through the brain blood barrier of adult animals, making possible the increase in the oxygen consumption of the brain by thyroxin. After many vain attempts, we frequently succeeded in doing so by pretreating animals for several days with pentobarbital (Nembutal). After this pretreatment the brain oxygen consumption of adult animals could also be considerably raised.

When studying these results it was tempting to speculate about the parallelism between the conditions under which the thyroid hormone can enter the brain of the young animal and the ease for education, learning, and the acquisition of normal or pathologic ideas by the young human brain. We were also tempted to ask whether the existence of a brain blood barrier is not similarly connected with the entering of some hormones in the brain, altering its metabolism, and with the fixation of some thought processes. Such considerations were also accompanied by consideration of the various forms of psychiatric abreaction. Of course, we still know very little about the nature of the brain blood barrier. However, should there be any probability in the evaluation made of the facts mentioned above, procedures that help us to break through the brain blood barrier would, in proper combination with biochemical and psychologic procedures, become of great therapeutic value in the future.

SUMMARY

A disturbance of the endocrine equilibrium becomes decisive in the development of mental disease only when the individual is subjected to various precipitating stress conditions. Then, owing to the restriction in the width of adaptation, the individual can break down and develop mental illness in accordance with the premorbid personality pattern.

Precipitating stress conditions and various standardized treatment procedures alike can produce changes in the endocrine function, which ought to be specified in order to understand success or failure in therapy.

Some basic changes in the endocrine function produced by various treatment procedures were studied in animal experiments.

The role played by the pituitary in acute stress conditions has been overestimated. Many acute stress reactions of the ductless glands are independent of the pituitary and are also not restricted to a change in the adrenal cortex function.

The uptake of radioactive phosphorus after electroconvulsive therapy, or other stress, is decreased in the thyroid but increased in the adrenal cortex and ovary. Identical changes occur in both normal and hypophysectomized animals.

The action of the pituitary anterior lobe after stress is more a regulatory response of the gland to the changes occurring during acute stress. One electroshock decreases the ACTH content of the pituitary and increases its thyrotrophic hormone content. One insulin coma seems to increase the ACTH content of the pituitary anterior lobe.

Chlorpromazine influences the hormone equilibrium to a considerable extent. After one injection, the I^{131} uptake rate of the thyroid is increased, adrenal cortex weight increased, ovary weight decreased, and the ACTH content of the pituitary increased.

A possible correlation between the existence of a brain blood barrier and the homeostasis developed in the brain to a higher degree than in other organs and the fixation of normal and pathologic thought is being discussed.

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Anxiety States in the Army Associated with Overactivity of the Thyroid

Brig. J. T. Robinson, O.B.E., M.D., D.P.M., Lt. Col. J. McGhie, M.B., D.P.M.,* Capt. E. Severs, M.B.,* M. Reiss, M.D., D.Sc.,† I. D. K. Halkerston, B.Sc.,† Janet C. Hillman, B.Sc.,† D. B. Palmer, B.Sc.,† and A. T. Rundle, B.Sc.†*

NETLEY AND BARROW GURNEY, NR. BRISTOL, ENGLAND

The acute psychiatric Army case seems to be particularly suitable for psycho-endocrine investigation, not because there is anything special in the symptoms encountered, but because in the Army similar stresses affect large numbers of servicemen in a relatively similar environment. From an etiologic point of view, the chief environmental influence is the Army life with its demands of discipline and training. This offers an opportunity to study, under similar conditions, endocrine adaptation in association with psychiatric changes in response to various precipitating causes in different personality types.

It has been shown[11, 12] that the same psychiatric symptom can be connected with different endocrine deviations and that, on the other hand, the same endocrine deviation can be associated with different psychiatric disturbances.

At present it is possible to progress only by means of longitudinal investigations on individual patients, correlating the endocrine and psychiatric changes observed. Where deviations from the normal endocrine pattern are found, it is now possible, with recent improvements in the methods of investigation and in the production of hormones, to normalize in some patients the endocrine disturbance and to study the effect of such change in the mental reaction of the patient.

This paper describes some psychiatric syndromes in which there were found concomitant endocrine disturbances and for which the appropriate hormone therapy was given and the effects on clinical progress studied in each case. The clinical changes were coordinated with the biochemical findings. In this respect, advantage is being taken of the relatively uniform Army situation for the purposes of these investigations. This uniformity cannot be readily obtained in civil practice because of the great variation of the environment.

One of the concomitant endocrine disturbances worthy of special mention but rarely encountered in clinical routine endocrinology, though not infrequently seen in psychiatric illness, is that of insensitivity of the body periphery to a particular hormone, the production of which is in or above the normal range. For instance, a relative insensitivity to thyroid hormone can occur when, although the thyroid activity as measured by the I^{131} tracer method is normal, or although the quantities of the hormone produced are even above the normal range, yet the basal metabolic

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This paper was written in cooperation with the Psycho-endocrine Research Group.

* Royal Victoria Hospital, Netley.

† Biochemical and Endocrinological Research Unit (South Western Regional Hospital Board), Barrow Gurney, Nr. Bristol.

rate is below the normal range[15] and the skin is dry and cold. This has already been described by Langfeldt[6] and Hoskins and Sleeper,[7] who found that patients in this state do not react with an increase in the basal metabolic rate even after treatment with high doses of thyroid hormone. There are other patients who, in spite of having normally developed gonads and an androgen excretion rate in or above the normal range, do not show any traces of a beard, while other secondary male sex characteristics either are not fully developed or are abnormal in some way, e.g., hair growth or distribution.

METHODS

Endocrinological Investigations. Every patient was thoroughly investigated clinically, and in none were gross clinically recognizable endocrine deviations found.

For several reasons, the scope of the investigations is at present rather restricted. It is inadvisable to subject certain patients to lengthy examinations and tests, owing to their psychiatric disturbance, while an unnecessarily prolonged period in the hospital renders it more difficult to return the patient to duty. Furthermore, the capacity of any endocrinological laboratory is at present limited as far as exact investigation methods are concerned.

We therefore restricted our investigations mainly to some essential data concerning the thyroid and the adrenal cortex.

Investigations of thyroid activity were carried out by the radioactive tracer method already described.[4] The normal range used for comparison was the same width of normal range as was found in previous investigations. The definition of the normal range is being further improved by the investigation of normal Army personnel serving in this hospital living under the same climatic, nutritional, and environmental conditions as the psychiatric patient.

The parameters previously described[4] illustrate the standards with which the numerical values found in the cases outlined below can be compared. These are as follows: K, the uptake slope of I^{131} during the first hour (increased value >3). R_e, I^{131} uptake by the thyroid in 24 hours in per cent of the injected dose (normal range 25 to 50 per cent). I_t, the thyroid index (ratio between R_e and K) (normal range 1.7 to 7.1).

It has been shown previously[4, 13] that the normal range of thyroid activity, as determined with this tracer method, is in more than 90 per cent of cases in agreement with the generally accepted normal range of the basal metabolic rate. In most cases, clear-cut under- and overactivity of the thyroid as assessed with the tracer method is in agreement with decreased and increased basal metabolic rate values, respectively. In a small number of cases where there was found to be no agreement between the value for the thyroid activity as determined by the tracer method and the basal metabolic rate (as already described above), undersensitivity of the body to thyroid hormone was assumed.

The great advantage of the radioactive tracer method over the basal metabolic rate determination lies in its suitability to detect borderline disturbances of thyroid function. At present, this is the most useful method for detecting early thyroid disturbance. This seems important if one considers the various psychiatric phe-

nomena that frequently occur in early stages of hypothyroidism[10] but that are only rarely correlated with thyroid disturbance.[12]

It must, however, be recognized that contrary to the basal metabolic rate determination, the radioactive tracer method cannot be repeated at intervals of less than three weeks. In using 25 μc. of I^{131}, as was done in these investigations, results in shorter time intervals are invalidated by I^{131} traces remaining in the thyroid from the previous determination.

The total 17-ketosteroids excreted in 24 hours was determined according to the method of Callow et al, 1939. The percentage of different 17-ketosteroid fractions in the total ketosteroids excreted was determined by a chromatographic absorption method on alumina (modification of the method of Dingemanse et al[2]).

The Psychiatric Assessment. The cases were clinically assessed at regular intervals by at least two psychiatrists independently. The changes seen are for the purpose of psychoendocrine correlation recorded in connection with the diagrams of the endocrine changes.

Only patients admitted to the hospital with psychiatric symptoms and signs are considered in this paper. Those suffering from any physical disease that might have complicated the picture were excluded.

It should be stressed that in all cases very careful attention was paid to psychotherapy and occupational therapy, hospital care, and dietary. These in themselves failed to produce any progressive improvement, but because of the various internal and external factors that can contribute to breakdown, it is considered that full use must continue to be made of all these accepted methods.

CASE HISTORIES

Case 1. Acute Anxiety State in a Basically Emotionally Immature Personality. A fair, pallid youth, aged 18 years, in the National Service, was admitted to the Royal Victoria Hospital on Aug. 17, 1954. He complained that he often felt nervous, was scared of the dark, had a sinking feeling in his stomach, diarrhea, and sweating, did not think he would settle down to Army life as he felt different from others, and disliked being away from home. He stated he could not "say things properly" and that he found difficulty in "picking things up," could not mix with the other recruits, and wanted to get away by himself.

A poor scholar, he disliked sports at school and was often the "butt" of his fellows. At about the age of 13 years he became a problem for his parents. He was impudent, rude, and at times became violently ill-tempered; he once assaulted his mother. All his family were relieved when he was called to the service. He had had three progressively better jobs prior to entering the Army. He had never had any interest in girls.

On examination, he was shy, anxious, restless, suspicious, timid, and markedly schizoid. He exhibited marked emotional lability; one moment he was smiling, the next blushing or in tears. His nails were severely bitten. His stream of talk was relevant, rational, logical, and coherent. There was no evidence of disordered thinking, but he spoke slowly. He seemed to have difficulty in understanding simple questions. His thought and mood were congruous, the latter fluctuating

rapidly from tears to smiles. He was well orientated in time and place; memory was intact and concentration unimpaired. He was below average intelligence (Matrix S.G. 5). There was no evidence of hallucinations or delusions.

Endocrine Investigation. The initial radioactive iodine thyroid test on this patient gave a 24 hour uptake of 74 per cent of the injected dose, a value usually associated with clinically recognizable hyperthyroidism. Other than a slightly increased pulse rate (108), the patient showed no signs of thyroid overfunction, and the basal metabolic rate was within the normal range (+4). Furthermore, his hands were cold and cyanotic. Although the patient's testicles and penis were of normal size, and the total 17-ketosteroid excretion rate was well within the normal range (13 to 15 mg./24 hours), he showed no signs of beard growth, while his trunk was also free from hair, except for scanty pubic hair with a feminine distribution.

The discrepancy between the tracer and basal metabolic rate results seemed to indicate a state of peripheral undersensitivity to thyroid hormone in this patient, and on this basis, treatment with nicotinic acid was instituted (100 mg. twice a day, increased later to three times a day). The results of the investigations are plotted in figure 1.

The general outline of the changes observed during treatment consisted in some increase of the total 17-ketosteroid excretion rate and a reduction of the high thyroid activity to within a normal range. These changes were accompanied by progressive mental improvement (see figure 1).

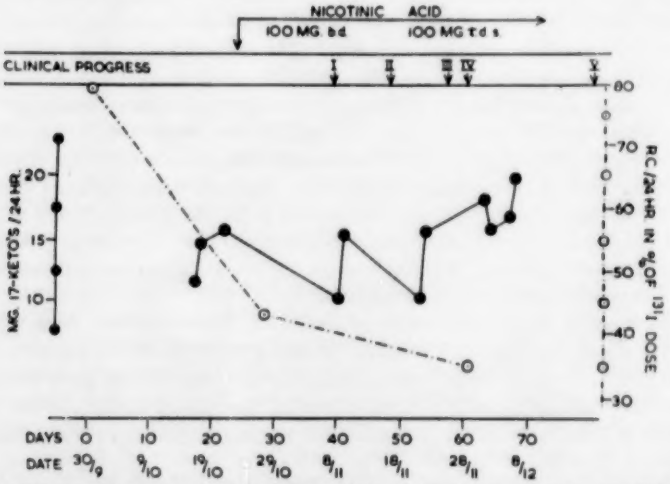

FIG. 1. Clinical progress in case 1. (I) Nov. 7, 1954—Little clinical change. (II) Nov. 16, 1954—Patient shaved for the first time in his life. Acne has appeared on face. Appears more cheerful. (III) Nov. 25, 1954—States he feels more confident in himself but is unwilling to go back into the Army. Basal metabolic rate + 8 per cent. Shaved today. Acne present on neck as well as face. (IV) Nov. 28, 1954—Patient looks well. Is happier and exhibits less tension and anxiety, still blushes easily. Shaved again today. Pubic hair distribution definitely male type. Definite clinical improvement. (V) Dec. 18, 1954—Improvement continues. Shaves every second day. (VI) Jan. 7, 1955—Normal hormonal equilibrium. Clinically no psychiatric disability. Discharged.

The most interesting clinical and endocrine changes observed were the development of acne and the commencement of beard growth after some four weeks of treatment.

Comment. The peripheral undersensitivity in this patient appears to be related to his psychoendocrine disturbance, and clinical improvement is correlated with the administration of nicotinic acid.

Case 2. Subacute Anxiety State with Acute Phobia. The patient, a 44 year old happily married officer, was admitted to the hospital on Nov. 5, 1954, complaining of acute panic attacks, fear of traveling in trains and buses, lack of self-confidence, vague headaches, muscular pains, and fear of fits. His symptoms had been present to a varying degree for about five years until finally he could not do his work and shunned all social contacts. He had had meningitis when 6 years old, which resulted in paralysis of the right upper limb. Since then he had had six typical attacks of jacksonian epilepsy commencing in the right hand. These attacks occurred at irregular

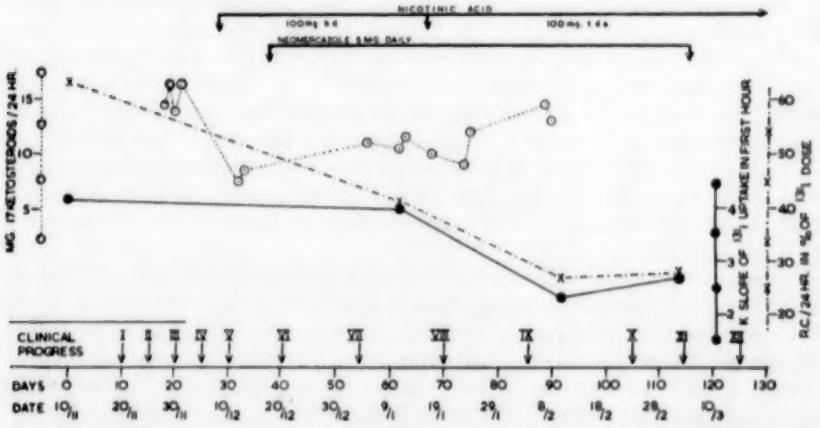
NICOTINIC ACID
100mg. 3 d.
100mg. 1 d.
MEPROBAMATE 2 MG. DAILY
MG. 17-KETOSTEROIDS / 24 HR.
K SLOPE OF I^{131} UPTAKE IN FIRST HOUR
R.C./24 HR. IN % OF I^{131} DOSE
CLINICAL PROGRESS
I II III IV V VI VII VIII IX X XI XII
DAYS 0 10 20 30 40 50 60 70 80 90 100 110 120 130
DATE 10/10 20/10 30/10 10/12 20/12 30/12 9/1 19/1 29/1 8/2 18/2 28/2 10/3

FIG. 2. Clinical progress in case 2. (I) Nov. 20, 1954—Clinical condition unchanged. On being informed that sedatives would be gradually stopped, he became acutely anxious and agitated. Tremor of lips increased. Pulse 80/minute; blood pressure 145/95. (II) Nov. 23, 1954—Electroencephalogram shows a dominant postcentral rhythm at 10 cycles/second that is of average voltage and blocks to visual attention. In the resting record, random 6 to 7 cycles/second waves are seen; on overbreathing, this theta becomes more prominent but shows no asymmetry. This is a mildly abnormal record, but there is no positive evidence of any abnormal focus. (III) Nov. 30, 1954—Remains tense, anxious, and agitated. (IV) Dec. 4, 1954—No clinical improvement. (V) Dec. 10, 1954—Feels the effects of vasodilators and complains of tingling sensation in hands and feet. Clinically there is no marked change, but he appears less agitated. However, he complains of fear of venereal disease. Pulse 120/minute. (VI) Dec. 20, 1954—Permitted to go home for Christmas leave, he became agitated and anxious and expressed fear of traveling. Demanded an orderly to accompany him but went on his own. (VII) Jan. 3, 1955—Returned from leave. Alleges severe headaches at home. Relieved to be back but complained of severe panic attack on train. Appears less tense, anxious, and agitated. (VIII) Jan. 19, 1955—Clinically he is improved. Subjectively there is little change—he complains of lack of self-confidence and panic attacks. States that he is rather breathless on exertion. Appears to like discussing and relating his subjective complaints. Pulse 110/minute. (IX) Feb. 4, 1955—Improvement continues. Patient states that he feels much better and sleeps well. Has occasional panic attacks during the day but these are less frequent and not so severe. (X) Feb. 23, 1955—Improvement continues. Panic attacks less frequent and now two to three times a week. (XI) March 8, 1955—Clinical improvement continues. (XII) March 15, 1955—Patient is much happier, sleeps well, and has maintained his clinical improvement. He was discharged fit for duty.

intervals; the last three he remembered were in 1938, 1939, and 1947. Since they started he had been on phenobarbitone, 0.5 gr. three times a day, and in addition, since 1947 he had been taking Sodium Amytal, 3 gr. nightly.

On admission the patient was tense, anxious, and very restless. He was emotionally labile, fluctuating between smiles and tears, and very ashamed of himself for bursting into tears. He complained of lack of self-confidence, pains in the back of the neck, palpitation, and sweating. His sleep was very restless in spite of taking the Sodium Amytal. His hands and feet were cold, his face pale; face and hands were sweating. Pulse rate was 80/minute; blood pressure was 140/90.

The most outstanding deviation observed in this patient was in the activity of the thyroid. He showed a markedly increased thyroid activity as measured by the radioactive iodine tracer method (see figure 2), but the basal metabolic rate was −14.

Because of the state of peripheral undersensitivity, he was treated first with Priscoline, 25 mg. twice a day, but later this was changed to nicotinic acid because he complained of headache with the former. The nicotinic acid appeared to have the effect of unmasking various signs suggesting hyperthyroidism, with tachycardia and palpitations, a resting pulse rate of 120/minute, and further increased tremor and sweating. To counter this, treatment with Neomercazole (No. 2 carbethoxy methimazole), 5 mg. daily, was begun, and this resulted in a gradual decrease in the thyroid activity (fig. 2). This change was accompanied by a corresponding clinical improvement and an alteration in the excretion rate of the total 17-ketosteroids.

This patient's showing on the psychologic test battery demonstrated no change in the basic pattern of his personality, but a great improvement in his condition was inferred from the lowering of defensive mechanisms as shown by the self-rating and by the insight test.

Comment. This patient apparently exhibited a combination of increased thyroid activity and a peripheral undersensitivity to thyroid hormone. The release of the latter resulted in a temporary exacerbation of symptoms and signs of hyperthyroidism, which responded to Neomercazole.

There is evidence from the clinical progress and the biologic findings before and during treatment that there is a relation between the endocrine state and the psychologic disturbances.

In the first few months of treatment the patient required daily supportive psychotherapy and discussions of his problems, in addition to Neomercazole and nicotinic acid.

Case 3. ***Acute Anxiety State with Phobic Features.*** A young, unmarried, regular senior noncommissioned officer, aged 24 years, with three years' service, complained of weakness, palpitations, hot and cold feelings, unaccountable panic attacks, and pains in the head. He had lost confidence in his capacity to do his work and felt acutely tense and anxious in the presence of superiors. These symptoms had been present for six months. He was treated in a hospital in Germany with modified insulin for three weeks in December, 1954, and was discharged fit to his unit. Within a week his symptoms returned more acutely than before, necessitating his readmission to the hospital and final transfer to the Royal Victoria Hospital, to which he was admitted on Jan. 19, 1955.

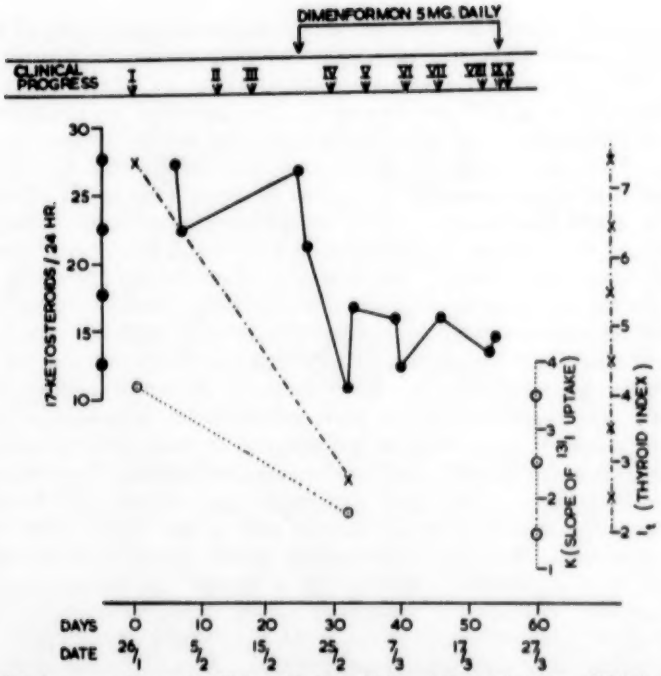

FIG. 3. Clinical progress in case 3. (I) Jan. 26, 1955—Malamud Rating Scale 19. (II) Feb. 8, 1955—Electroencephalogram and roentgenogram of skull reveal no abnormality. Clinical condition remains unchanged. (III) Feb. 13, 1955—Exhibits some obsessional ruminative traits and objectively little improvement. (IV) Feb. 25, 1955—Subjective improvement marked. He states that he feels much happier and contented. Concentration is better. Still sweats on hands and feet. Sleeping well. (V) March 2, 1955—Clinical improvement continues. Is much more cheerful and optimistic. (VI) March 8, 1955—Appears anxious. Feels he is relapsing and had a brief panic attack. Readily accepts that he has not relapsed but that his earlier improvement following injections was more apparent than real. (VII) March 13, 1955—Clinically he is well and cheerful, is contented, keeps himself busy in occupational therapy, and assists in the ward work. (VIII) March 20, 1955—Clinical improvement maintained. (IX) March 22, 1955—Malamud Rating Scale 8. (X) March 23, 1955—Discharged to unit in Category S.7—for review in three months.

Examination revealed a tidy, neat, clean-shaven, flabby youth with pale face, of high intelligence, who was tense, anxious and agitated, and very restless. He spoke rapidly and precisely but showed no disturbance of thought processes. He exhibited some acne vulgaris on face, neck, and shoulders; there was tremor of the fingers and sweating of the hands and feet. His extremities were cold. Blood pressure was 140/85.

Due to parental friction he had had an unsettled though happy childhood. His sister was in a colony for mental defectives. His maternal grandmother had died in a mental hospital.

Endocrinological Investigations. The most outstanding changes observed in this patient were a total 17-ketosteroid excretion rate above the normal range. The percentage of dehydroandrosterone was very high.

The 24 hour I^{131} uptake of the thyroid of this patient was, at the time of measurement, in the normal range, but the summit of I^{131} uptake was apparently reached some hours before, as the uptake rate in the first hour (K) was considerably increased, resulting in an I_t above the normal. This permitted the conclusion of an increased I^{131} turnover (see figure 3), which in this case was accompanied by clinical symptoms of sweating, feeling hot, palpitations, and panic attacks.

The endocrine deviation seemed to indicate an overactivity of the pituitary anterior lobe, and on this assumption it was decided to try the effect of treatment aimed at suppressing this activity. Accordingly the patient was given 5 mg. of estradiol benzoate (Dimenformon) daily. Five days after treatment was begun, the thyroid activity and the 17-ketosteroid excretion rate were reduced to normal range. At the same time the patient assured his doctors that subjectively he felt much better. Objectively there was marked clinical improvement, which continued to such a degree that he was sent back to his unit fit for duty. He is still serving.

Comment. The severe tension and panic attacks failed to respond to modified insulin and psychotherapy. When he was admitted to the hospital, a vicious circle had apparently developed with emotional tension, accompanied by pituitary overactivity with increased production of thyrotrophic and corticotrophic hormone, resulting in increased activity of the thyroid and adrenal cortex. The increased amount of hormones released by these glands would appear to be related to the persistence of this patient's symptoms. It is known that estrogen can depress pituitary anterior lobe function. This hormone was therefore used in an attempt to interrupt the vicious circle described, and it produced a rapid restoration of hormone equilibrium associated with clinical improvement. Apparently, the application of therapy based on the biologic findings coincided with clinical improvement.

Case 4. Acute Anxiety State with Compulsive Features and Impotence. A junior noncommissioned officer, aged 20 years, married, above average intelligence, with six months of Army service, was admitted to the Royal Victoria Hospital on Sept. 14, 1954, with severe acute anxiety features. On examination the patient was very tense, anxious, and agitated. He walked with a slow hesitant step, and when asked to sit down, placed himself on the front edge of the chair, where he kept fidgeting, wringing his hands, and biting his nails. He appeared unhappy, suspicious, and frightened. He exhibited marked tremor of the lips and hands. He spoke in a dull, monotonous, soft, and petulant voice, and was clearly most reluctant to discuss his problems. His talk, however, was rational, relevant, logical, and coherent. There was no evidence of disordered thinking. His mood was one of misery and self-pity, and throughout the interview he was in tears. Mood and thought content were congruous. There was no evidence of ideas of reference or influence, hallucinations, or delusions; he was well orientated in time and place. His hands were moist, but no other physical signs were elicited.

In addition, he complained of compulsive urges to wear women's clothing, and of impotence with his wife. The former had been present since the age of 6 years when he used to sleep in his parents' bedroom and put on either his mother's or sister's underclothes. This urge to which he had succumbed had been present two or three times a week ever since. He was married six months previous to this examination

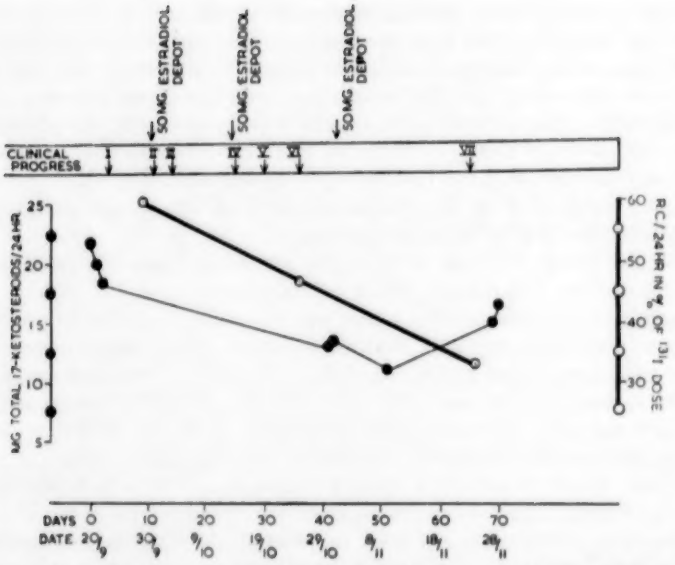

FIG. 4. Clinical progress in case 4. (I) Sept. 23, 1954—No clinical change. Malamud Rating Scale 20½. (II) Oct. 1, 1954—Patient still tense. (III) Oct. 4, 1954—Anxious, agitated, sleeping badly, poor appetite. Weepy and querulous. Malamud Rating Scale 19½. (IV) Oct. 15, 1954—Clinical condition unchanged. (V) Oct. 20, 1954—Patient happier. Sleeping and eating well. Some tension still present, absence of tearfulness. (VI) Oct. 26, 1954—Marked improvement. Patient is happy. Sits calmly without tension and states that his sexual relationships with his wife have been perfect during the week end. (VII) Nov. 29, 1954—Discharged to full duty. Malamud Rating Scale 2. (VIII) June 1, 1955—Continuous serving with no symptoms.

to a girl who knew about his compulsion. Since then he had frequently dressed up in his wife's underclothes.

On all these occasions he would wear the garments for about 15 minutes, frequently having an erection, but he denied having any ejaculations. The wearing of these garments relieved his emotional tension, but he became harassed by thoughts that he would like to become a woman. He complained that his marriage was in danger of breaking up because his sexual relations with his wife were hopeless, and he had had no proper sexual intercourse since marriage.

The patient did well at school, obtaining a school-leaving certificate at the age of 16 years. He had had steady work as an apprentice plumber and pipe fitter before joining the Army. Until his admission to the hospital, he had had an excellent service record.

While overseas in Germany he became acutely worried about his condition and was admitted to a hospital, and then transferred to the Royal Victoria Hospital with the psychiatric opinion, "I doubt if this soldier will be able to complete his service, in view of his psychopathology which requires prolonged and skilled psychotherapy!"

Endocrinological Investigation. This patient showed an increased thyroid activity

as determined by the tracer method, while his 17-ketosteroid excretion rate was slightly above normal. These findings suggested an increased activity of the pituitary anterior lobe. Consequently, in order to depress this activity, the patient was treated with long-acting estradiol undecylate (estradiol depot, Schering) injected intramuscularly. Following this, the thyroid activity gradually came down to the normal range and the total 17-ketosteroid excretion rate also fell, but the dehydroandrosterone fraction of the 17-ketosteroid showed a rise (fig. 4).

Comment. Suppression of the pituitary activity of this patient with estradiol undecylate restored the hormone equilibrium.

The careful dosage of estrogen did not affect the patient's sex drive, but suppressed his neurotic disturbances, which were apparently related.

The endocrine disturbance in this case was very similar to that in case 3. His psychiatric disturbance, however, was more chronic, and in addition was complicated by some compulsions and by impotence. The patient was treated on the same principles as were used in case 3, the only difference being that an estradiol depot preparation was used. This long-acting preparation is of value in patients in whom injections produce additional stress that might delay the establishment of hormone equilibrium. As can be seen from figure 4, he had three injections during his entire stay at the hospital. In his case mental improvement accompanied the normalizing of the hormone equilibrium. In order to maintain the latter it was arranged, on discharge from hospital to unit, to give the patient one injection of estradiol depot every eight weeks. A recent review of the patient shows that improvement has been maintained and that he still retains potency.

Case 5. Acute Anxiety State in a Schizoid Personality. A National Service private with 18 months of service, aged 20 years, was admitted to a hospital in Germany on April 2, 1954, following a suicidal attempt by swallowing aspirin. He was transferred to the Royal Victoria Hospital on June 16, 1954.

On examination, he was very anxious, restless, agitated, and tense, and exhibited facial twitching and sweating of the palms. His stream of talk was relevant and rational, with some circumstantiality and a tendency to verbosity and vagueness. Concentration was impaired, and memory intact. In mood he was mildly depressed, but there was no incongruity. He was well orientated and had no hallucinations or delusions. Physically, nothing abnormal was detected.

From early childhood he had shown emotional instability and behavior disorder, necessitating frequent changes of school and outpatient psychiatric treatment. His mother was a chronic alcoholic who had been placed in a mental hospital and who eventually committed suicide. His only sibling, a younger brother, was for years under the care of a child guidance clinic.

Endocrinological Investigation. The predominant disturbance in the hormone equilibrium of this patient was a considerably increased thyroid activity; the ketosteroid excretion rate was in the upper borderline of the normal range, and the androsterone excretion rate was very high, while only very little dehydroepiandrosterone (in per cent of the total 17-ketosteroids) was excreted. The patient was treated with estradiol benzoate, 10 mg. daily, in order to reduce the thyroid activity on the basis that in association with the high excretion rate of total 17-ketosteroids, the thyroid

overactivity might be due to pituitary hyperfunction. However, the thyroid activity was little affected, remaining high in spite of this treatment. No clinical change could be observed, even though the total ketosteroids decreased. For this reason, it was assumed that the increased thyroid activity in this case was a primary hyperfunction of the thyroid itself and therefore Neomercazole treatment was

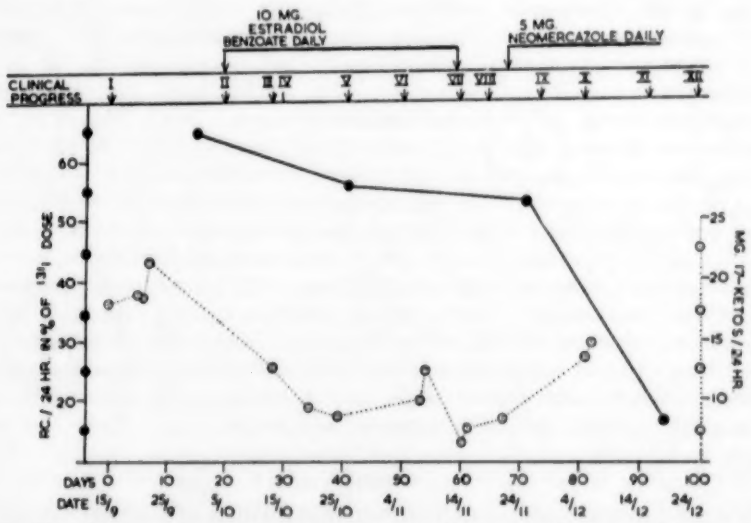
10 MG. ESTRADIOL BENZOATE DAILY
5 MG. NEOMERCAZOLE DAILY
CLINICAL PROGRESS
I II III IV V VI VII VIII IX X XI XII
RC. / 24 HR. IN % OF ^{131}I DOSE
MG. 17-KETOS. / 24 HR.
DAYS 0 10 20 30 40 90 60 70 80 90 100
DATE 15/9 25/9 5/10 15/10 25/10 4/11 14/11 24/11 4/12 14/12 24/12

FIG. 5. Clinical progress in case 5. June 17, 1954—Appears mildly mentally depressed and agitated and exhibits flattening of affect. July 3, 1954—Clinical condition deteriorated. Transferred to closed ward. July 7, 1954—Confused, agitated. Religiously ruminative. Very emotional and tense. Deep sedation begun (Sodium Amytal, 6 gr. three times a day). July 16, 1954—Temperature 103 F.; pulse 120/minute. Clinical evidence of right-sided lower lobe pneumonia. Penicillin given—slightly more confused mentally. July 18, 1954—Initially greatly improved. Not agitated. Less anxious and tense. Pneumonia improving. July 27, 1954—Clinically improved, mentally and physically. Aug. 6, 1954—Mental condition deteriorated. He is tense, anxious and agitated, and confused. Aug. 7, 1954—Tension very severe. Emotionally very upset. Chlorpromazine ordered. Aug. 10, 1954—Chlorpromazine stopped as white blood count dropped to 2700/cu. mm. Mental condition unchanged. Aug. 16, 1954—Clinical condition improved. Allowed home two weeks under care of parents. Aug. 31, 1954—Returned from leave. More cheerful and cooperative and for first time took part in ward activities. Sept. 7, 1954—Although better than when first admitted, he is still tense, anxious, and agitated. These symptoms are easily aroused by minor stimuli. (I) Sept. 14, 1954—Extremely tense, nervous, and distressed. Difficulty in expressing himself. (II) Oct. 4, 1954—Patient is restless and agitated. Exhibits some twitching of the face, tremors of lips and fingers. Acne on face. Emotionally labile and wept at interview. Some flattening of affect. Insomnia. Malamud Rating Scale 21½. (III) Oct. 9, 1954—No clinical change. Restless sleeper. (IV) Oct. 12, 1954—Appears happier. Subjectively feels much better. Objectively there is little difference. (V) Oct. 26, 1954—Subjectively and objectively improved. Not agitated or restless. No tremors. Sleeping better. Oct. 29, 1954—Improvement continues. Malamud Rating Scale 14. Nov. 2, 1954—Returned from leave. Very restless and agitated. Had an emotional outburst at home yesterday when he threw a cup of tea at the wall after argument with his step-mother. (VI) Nov. 5, 1954—Little improvement. Remains restless, agitated, and emotionally labile. Malamud Rating Scale 24. (VII) Nov. 12, 1954—Clinical condition unchanged. In an impulsive outburst of bad temper he threw a plate at the wall. (VIII) Nov. 19, 1954—No clinical improvement. Very nervous and tense. Continually puts his hand to his mouth when talking. (IX) Nov. 26, 1954—Clinical condition remains unchanged. (X) Dec. 5, 1954—Appears less agitated and tense. Still remains "asocial." Concentration still impaired. (XI) Dec. 18, 1954—Objectively shows clinical improvement. Less anxious. Optimistic about his future and very sociable. (XII) Dec. 23, 1954—Discharged from hospital much improved. Feb. 10, 1955—Patient appears confident and happy and exhibits no clinical evidence of any psychiatric disability.

started, after which the thyroid activity was reduced and the excretion rate of the 17-ketosteroids remained within the normal range. Clinically the patient improved, and follow-up three months later showed that improvement was maintained. (See figure 5.)

Comment. Estradiol benzoate produced a reduction of the total 17-ketosteroid excretion rate without affecting any clinical improvement or altering the activity of the thyroid. This seemed to indicate a primary thyroid overactivity, for which Neomercazole was prescribed. The administration of the latter resulted in a gradual return of the thyroid to normal, accompanied by clinical improvement.

The patient was discharged into a quiet civilian job, and continued treatment with Neomercazole, 5 mg. daily. He has been doing very well in his job. About two months after discharge he returned to the hospital for check-up, and his thyroid activity was tested again and found to be high. However, at this time he did not show psychiatric symptoms. The only explanation for this is the fact that the stress conditions in the patient's civilian job were not now so severe as those that initially precipitated the psychiatric disturbances in association with disturbed hormone equilibrium and the reduced width of adaptation of this patient. His present occupation is in better harmony with the reduced adaptability of this patient. A further check showed that the thyroid activity is now well within the normal range, and this patient's clinical improvement is maintained. This was confirmed by a recent communication from his father. He is on a maintenance dose of Neomercazole, 5 mg. every third day, and will be rechecked at intervals.

DISCUSSION

In this paper, 5 patients are described who had a variety of psychiatric symptoms that were accompanied by disturbances in hormonal equilibrium in which a predominance of thyroid deviations was demonstrated. Common to all were signs and symptoms of anxiety, while the predominant thyroid deviation in each was overactivity. Hemphill[6] draws attention to the fact that anxiety is generally believed to be basically responsible for hyperthyroidism, unless the picture is colored by delirium derived from excessive thyroid intoxication. In the 5 cases presented here, there was nothing clinically to suggest hyperthyroidism and in none was there any evidence of thyroid enlargement. It is relevant to point out that investigations of thyroid function in the male mental hospital population of Bristol indicate a definite tendency to hypothyroidism.[14] It is, of course, extremely difficult to decide on causal relationships between endocrine disturbance and psychiatric symptoms, owing to the complexity of the various factors concerned with mental breakdown. The precipitating cause may be primarily responsible for the change in endocrine equilibrium. Or, the endocrine equilibrium may have been initially disturbed so that mild precipitating factors produced mental breakdown because of the narrow adaptation of the individual, whose vulnerable basic personality could not stand up to additional small stresses that are resisted by others without difficulty. We are in agreement with Hemphill[6] that the demonstration of undeniable endocrine disturbances does not authorize the claim that they have a causal relationship with mental symptoms. These few cases merely indicate a relationship between psychiatric symptoms and

overactivity of the thyroid in which the restoration of hormonal equilibrium coincided with recovery of the mental symptoms.

Cases 1 and 2 show similar peripheral undersensitivity to thyroid, the pathogenesis of which is not yet known. This state has not been reported in other than psychiatric patients.[4]

Patients showing peripheral undersensitivity to thyroid hormone appear to suffer in effect from a mild form of hypothyroidism. Their tissues are unable to increase the rate of oxidation sufficiently whenever necessity arises (e.g., change of temperature). It is possible that such a reduced capacity to utilize thyroid hormone acts like any other hormone deficiency in the periphery, and it is apparently due to the neuroendocrine feed-back mechanism that more thyrotrophic hormone is produced under such conditions. It is believed that an equilibrium is preserved between the anterior pituitary and the thyroid through the concentration of thyrotrophic and thyroid hormones in the blood. Thyrotrophic hormones increase the secretory activity of the thyroid, but the thyroid hormone inhibits the thyrotrophic activity of the anterior lobe of the pituitary.[9]

It might well be that in the 2 cases described above the peripheral undersensitivity for thyroid hormone was the primary cause for the thyroid hyperfunction found. Such an assumption gets some support from the fact that the thyroid activity in case 1 was reduced to normal range by treatment with nicotinic acid only.

Neither of these 2 patients showed any clinical symptoms of vitamin deficiency. Gregory[3] has comprehensively reviewed the action of nicotinic acid, and has pointed out the multitude of conditions in which nicotinic acid can be used beneficially in psychiatry. The action of this substance on the peripheral hormone undersensitivity described may indicate an important role of this substance in endocrine equilibrium.

Case 4 shows how careful one should be in the endocrinologic approach to the symptoms of impotence. The present-day practice of those attempting the cure of impotence is to use psychoanalysis or to experiment with the use of the male sex hormone. It is seldom that disturbances of other glands are considered; in particular,[9] it would seem appropriate to investigate the thyroid function in cases of impotence when such patients excrete 17-ketosteroids in or above the normal range.

When surveying the endocrinologic investigations carried out on these patients, it should be emphasized that they still represent only initial attempts in endocrine investigations to analyze the psychoneuroendocrine interrelation. Estimation of the corticoids of these patients could not be carried out systematically; so the investigation of the adrenal cortex activity must be regarded as incomplete since 17-ketosteroid results indicate changes in only some of the adrenal cortex functions. Further, it would have been valuable to determine the concentration of the pituitary anterior lobe hormones in the body fluids instead of making only indirect deductions about their production, but routine methods are not yet available, being still in the developmental stage. Nevertheless, this restricted investigation of the changes in the thyroid gland and adrenal cortex associated with psychiatric changes appears to throw some further light on the significance of the endocrine equilibrium in psychiatric disturbances. Although this paper describes a number of cases with vary-

ing psychiatric disturbances treated on the basis of endocrinological investigations, we would stress that we are not advocating any general hormonal therapy in such cases but only attempt to describe a logical approach to a rational treatment, rather than one resting on an empiric basis, as is so common in psychiatry today. Furthermore, it should be stressed that no such therapy should be attempted unless investigations indicate that their use may help to restore biologic equilibrium. The latter is, however, only one among many factors found disturbed in mental illness. This is important since the restoration of biologic function greatly assists the psychiatrist in maintaining a progressive psychotherapeutic rehabilitation program and helps the patient to face up to his problems and adjust better to his environment.[15]

SUMMARY

Overactivity in the thyroid gland in association with varied psychiatric symptoms is described.

Patients were treated on the basis of their metabolic disturbances.

Clinical progress was correlated with changes in the function of the thyroid and adrenal cortex.

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Relaxant Effects of Meprobamate in Disabilities Resulting from Musculoskeletal and Central Nervous System Disorders

CLINICAL OBSERVATION OF FIFTY-FIVE CASES

Harriet E. Gillette, M.D.

DIRECTOR, PHYSICAL MEDICINE AND REHABILITATION CLINIC; AREA CONSULTANT IN PHYSICAL MEDICINE, VETERANS' ADMINISTRATION

ATLANTA, GA.

Rehabilitation after physical disablement involves total adjustment of the individual to the handicap, so that he can ultimately be restored to a useful social and economic status.[1] An extremity that has become useless from injury or disease may have muscles that are still functional and capable of limited activity. In the victim of congenital defect, or pre- or paranatal cerebral injury, some innervation may have survived in the damaged structure; the problem in these cases, therefore, becomes one of habilitation, with maximum cultivation of the patient's potentialities.[2]

Accidents on the highways and in industry, and also the stress of modern life, are responsible for many of the musculoskeletal disorders seen by the physiatrist. About 85 per cent of the injuries suffered by motorists in one series[3] involved the neck, back, and lower extremities. Two-thirds were so-called sprains, and about one third of these were the typical "whiplash" injuries caused by collisions from the rear. A pre-existing osteoarthritis of the cervical spine may serve to increase the vulnerability of automobile accident victims to neck injuries, and to prolong the disability.[3] Painful strains, with muscle spasm and limitation of movement from hyperextension of the lower back, are also common in everyday life.[4] After amputations, limitation of motion of the proximal joints by spasm or contracture may interfere with proper fitting and adjustment to the use of prostheses.

Cerebral palsy, a condition that is perhaps the most complex in etiology and diversified in manifestations of all abnormalities originating in lesions of the central nervous system, is believed responsible for about 6 per cent of crippled children in the country today.[5] Although such patients present extraordinary problems in development and adjustment,[6, 7] a well rounded therapeutic program[8] now offers them more help than was formerly available. Physiatric measures are also required for patients with paralyzed, spastic limbs after cerebrovascular accidents or injuries to the brain, to relax the contracted muscles and relieve discomfort.

In any long term disability, emotional stress may seriously complicate the case.[9] General anxiety is often a part of the clinical picture in neuromuscular disturbances,[10–12] and in some patients with central nervous system lesions accompanied by severe physical, but little or no intellectual, impairment, emotional maladjustment may retard maximum habilitation.[13]

To differentiate between muscle tonus and spasticity as seen in central nervous system disorders is not a simple matter, and in musculoskeletal disabilities, it is also

very difficult to distinguish the role of emotional tension in the production of spasm from true muscular contraction itself. Massage, exercise, and other physiatric measures are necessary to relax, strengthen, and increase the contractile range of muscles that, because of mechanical factors or nerve root irritation, are maintained in a continued state of shortening, and such procedures also have a part in the relief of anxiety and nervous tension.[14]

Although drugs have been used for many years to supplement physical therapy, none have satisfactorily filled the urgent need of an agent capable not only of central tension-lessening effect, but also of direct action on the contracted muscle. Many preparations have been introduced for alteration of tonus, but after prolonged trial it has become clear that most are of little or no value[15] and that early favorable reports were based on wishful thinking. Certain of these agents are not well absorbed and lack effect. Others, although possessing more or less efficient muscle-relaxant properties, produce respiratory depression and have other undesirable side actions[16] that render them unsafe for long-continued use. Certain substances developed for specific purposes displayed an ability to relax muscle tonus as a secondary action, but these, too, were attended by disadvantages. (An example is diphenylhydantoin, which was produced for control of grand mal seizures. This drug will reduce tonus, but at the expense of causing gingivitis and ataxia.)

Tranquilizing action has been claimed for certain of the piperidyl compounds[17] and for derivatives of *Rauwolfia*, and relief of spasticity as well has been attributed to one of the amine derivatives of phenothiazine (chlorpromazine[18]) and to some other substances. All are inconsistent in effect,[17] and the value of the usually transient relaxant action[18] of chlorpromazine on the muscles may be limited in long term administration by risk of changes in the blood picture, jaundice, hypotension, tachycardia, and sensitivity reactions.

Meprobamate, the dicarbamate of 2-methyl-2-*n*-propyl-1, 3-propanediol[19] (one of the compounds derived from the 1,3-propanediols[20]), has exhibited considerable promise for relief of neuromuscular spasm. Animal and clinical investigations[19, 21–24] have demonstrated definite relaxant properties completely unlike those of any other tension-reducing agent known. The compound appears to exert a selective blocking action on the long interneuronal circuits of the central nervous system,[21] particularly between the cortex and thalamus. Definite synchronization of the brain waves, with moderate slowing in frequency, is shown on the electroencephalographic tracing. Psychic as well as muscular stress is alleviated without altering the action of the autonomic mechanism. Heart, lung, and gastric secretory functions and the excretion of sweat are not interfered with; no effect is produced on the peripheral nerves or myoneural junction. In a recent clinical study[25] of ambulatory patients suffering from neuromuscular tension, it is reported that the electromyogram indicated an improved capacity for voluntary relaxation, with more efficient coordination of muscle action, after medication with meprobamate, as well as a noticeable amelioration of emotional strain.

PLAN OF STUDY

A series of 55 clinic patients, divided into two groups, received meprobamate

(Equanil*) as an adjunct to the physiatric management indicated in each particular case.

Group 1 (table I) comprised 27 cases of musculoskeletal disorders, including (a) 13 patients suffering from cervical myositis and fibromyositis, bicipital tendonitis, and painful muscular spasm of back, arms, and hands, caused by trauma or psychogenic stress or both; (b) 4 with herniated intervertebral disc; (c) 7 patients with whiplash injuries; (d) 1 suffering from rheumatoid arthritis and rheumatic heart disease; and (e) 2 patients with muscle spasm and contracture in both shoulders following bilateral amputation of forearms and hands.

Spasm and stiffness had been present in the arthritic patient for many years; in the 7 with whiplash injuries, for one week to one year; in those with cervical myositis, bicipital tendonitis, and the like, for one month to 15 years. The patients with herniated intervertebral disc had experienced recurrent episodes for 2 to 10 years, with the presence of symptoms in the attack under treatment for one to six weeks, and the amputees had suffered their mutilating accident three and one-half years previously in one case and four months previously in the other.

Group 2 (table II) included 28 patients whose neuromuscular disturbances were the result of central nervous system lesions caused by pre- or paranatal cerebral damage.

Eight adult hemiplegic patients were undergoing rehabilitation. Seven (aged 50 to 68 years) had been paralyzed two months to five years or more as a result of cerebrovascular accident, and 1 had had a brain tumor removed three months previously.

Two patients were severely paralyzed as a result of injuries received in automobile accidents. Patient no. 25, a 9 year old boy, was completely incapacitated, with severe flexor spasticity and contractures.

Sixteen patients were afflicted with cerebral palsy (12 of athetoid and 4 of spastic type). In this group were 4 children whose mental and physical deficiencies were so severe that their condition was apparently hopeless.

Two adolescent females had dystonia musculorum deformans progressiva.

DOSAGE

Initially, the dose recommended for the adult patient was 800 mg. three times a day. However, medication in this amount caused drowsiness in some cases. The hemiplegic patients became too somnolent and showed a loss of motivation. The dose then was adjusted to 400 mg. three times a day for all adolescent and adult patients, regardless of the diagnosis. An exception was made in the case of patients suffering severe spasm and pain. For these, the dose was increased as necessary. Four patients (of whom 1 had severe low back pain, nervous tension, and insomnia and 1 had herniated cervical disc, scoliosis, and kyphosis of several years' standing) received 400 mg. four times a day. One with a fractured shoulder, 1 with reflex dystrophy of the shoulder of four weeks' duration, and 1 with a whiplash injury of three weeks' duration required 800 mg. three times a day.

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* The trade name of Wyeth, Inc., for meprobamate is Equanil. Equanil Tablets were kindly supplied to us by Wyeth, Inc.

TABLE

27 Cases of Musculoskeletal Disease Accompanied by Spasm, in

No.	Patient	Sex	Age, yr.	Diagnosis	Symptoms and findings	Duration of condition	Duration of treatment	Therapy alone	Therapy plus drug	Daily dose schedule, mg.	Total daily dose, Gm.
1	M.S.	F		Cervical fibromyositis, whiplash	Tension synd.; induration cerv. muscles	7 mo.	2 mo.	1 mo.	1 mo.	400 t.i.d.	1.2
2	E.R.	M	61	Fractured shoulder	Severe spasm, induration cervical musculature	2 mo.	4 mo.	1 wk.	4 mo.	800 t.i.d.	2.4
3	E.M.	F	52	Reflex dystrophy, shoulder	Severe emotional tension; resistant contracture	1 mo.	8 mo.	4 mo.	4 mo.	800 t.i.d.	2.4
4	C.K.	F	52	Cervical fibromyositis	Tension headaches; moderate induration and spasm	4 mo.	2 wk.	1 wk.	1 wk.	400 t.i.d.	1.2
5	F.C.	M	38	Cervical fibromyositis	Headaches, induration, spasm	1 yr.	4 wk.	2 wk.	2 wk.	400 t.i.d.	1.2
6	F.H.	F	70	Cervical radiculitis, peritendonitis	Pain in neck, lt. should. Spasm, contract. of should.	2 mo.	4 wk.		2 wk.	400 t.i.d.	1.2
7	L.M.	M	52	Acute myositis, cervical, lumbar	Pain in neck, shoulders, hips	6 wk.	3 wk.	1 wk.	2 wk.	400 t.i.d.	1.2
8	D.M.	F	46	Cervical myositis, skull fracture	Pain, spasm, induration cervical musculature	2 mo.	3 wk.	1 wk.	2 wk.	400 t.i.d.	1.2
9	J.S.	M	52	Fibrositis, tension syndrome	Low back pain, cramping	5 yr.	6 wk.	2 wk.	4 wk.	400 q.i.d.	1.2
10	M.H.	F	51	Fibrositis	Extens., severe indur. Pain throughout back	15 yr.	5 wk.	1 wk.	4 wk.	400 t.i.d.	1.2
11	H.S.	F	55	Frozen shoulder	Severe contracture, moderate spasm	8 mo.	2 mo. (cont.)	2 wk.	6 wk. (cont.)	400 t.i.d.	1.2
12	M.D.	F	46	Frozen shoulder	Severe spasm and pain	9 mo.	3 mo. (cont.)		3 mo.	400 q.i.d.	1.6
13	N.C.	F	42	Frozen shoulder	Resistant contracture, moderate spasm	3 mo.	3 mo.	3 wk.	3 wk.	400 t.i.d.	1.2
14	P.P.	M	67	Shoulder-hand syndrome, osteoarthritis	Severe spasm neck, shoulder	6 mo.	3 mo.	1 mo.	2 mo.	400 t.i.d.	1.2
15	J.W.	F	38	Cervical disc	Severe spasm	1 wk.	1 wk.	2 days	5 days	400 t.i.d.	1.2
16	S.M.	M	31	Cervical disc	Severe spasm	1 wk.	10 days		10 days	400 q.i.d.	1.6
17	S.G.	M	31	Cervical disc	Severe spasm	2 wk.	4 wk.	2 wk.	2 wk.	800 t.i.d.	1.2
18	M.F.	F	52	Lumbar disc	Recurr. episodes. Present attack mod. spasm	6 wk.	6 wk.	3 wk.	3 wk.	400 t.i.d.	1.2
19	L.L.	M	45	Whiplash injury, osteoarthritis	Moderate spasm, severe induration	6 wk.	2 mo.		2 mo.	400 q.i.d.	1.6
20	R.L.	F	44	Whiplash injury	Recurrent episodes, severe spasm	1 yr.	3 mo.	1 mo.	2 wk.	400 t.i.d.	1.2
21	J.R.	M	25	Whiplash injury	Moderate spasm, headache	4 wk.	6 wk.		6 wk.	400 t.i.d.	1.2
22	R.B.	M	21	Whiplash injury	Moderate spasm, neck and back	8 days	5 wk.	1 wk.	4 wk.	400 t.i.d.	1.2
23	B.M.	F	41	Whiplash injury	Moderate spasm, severe induration	4 mo.	4 wk.	1 wk.	3 wk.	400 t.i.d.	1.2
24	S.P.	F	39	Whiplash injury	Very severe spasm	3 wk.	1 wk.		1 wk.	800 t.i.d.	2.4
25	M.L.	F	34	Rheumatoid arthritis	Severe contractures, moderate spasm	Many years	1 yr.	8 mo.	4 mo.	400 t.i.d.	1.2
26	J.S.	M	50	Reflex dystrophy of shoulder	Arm amputee; spasm, phantom pains	3 yr.	3 yr.	2½ yr.	6 mo.	400 t.i.d.	1.2
27	L.L.	M	41	Reflex dystrophy of shoulders	Bilat. hand amput.; mod. spasm of shoulders	4 mo.	1 mo.		1 mo.	400 t.i.d.	1.2

1

Which Meprobamate Was Used as an Adjunct to Physiotherapy

Clinical response									
Spasm		Pain		Emotional tension		Joint range			
Therapy	Therapy plus drug	Therapy	Therapy plus drug	Therapy	Therapy plus drug	Therapy	Therapy plus drug	Side effects	Remarks
++	++++	++	++++	+	++	++	++++	0 Euphoria, drowsiness	Abrupt improvement in response on addition of drug
++	+++	+	++	+	++	+	+++	0 Initial drowsiness	Init. tranquil. effect lost after 1st mo. Musculoskeletal effect persisted
+	+++	+	+	0	+	+	++	0	Good control of spasm, no effect on fibrous contracture
+	+++	+	+++	+	+++	++	+++	0	Recurrence of spasm on omission of drug for 3 days
++	++++	++	++++	+	++++	++++	++++	0	Tranquilizing effect significant in improvement
	++		0		+		++	0	No effect from meprobamate. Pain ceased with steroids
++	++++	++	++++	+	++	+++	++++	0	Rapid response to drug
++	++++	++	++++	++	++++	++	++++	0	Prompt response to drug
++	++++	++	++++	++	++++	++	++++	0	Prompt response with control of emotional tension
+++	++++	+++	++++	++	++++	++	++++	0	Delayed response, eventual result good
+	++	++	++	+	+++	+	+	0	Stretching tolerated better with drug
	+++		++		++		++	0	Spasm quickly controlled
++	+++	+++	++	++	+++	++	+++	? Withdrawal sym.	Headache, nausea on cessation of drug
++	+++	++	++	+	++	++	++	Erythematous, itching, rash of hands	Rash ceased on stopping drug
++	++++	+++	+++	+	++	++	+++	0	Spasm quickly controlled
	+++		+++		+		+++	0	Satisfactory control of symptoms
++	++++	++	++++	+	+	+++	++++	Drowsiness	Phenylbutazone used 1st with little effect. Spasm control in 24 hr. with meprobamate
++	++++	+++	++++	+	+	++	++++	0	Complete conservative program enhanced with addition of meprobamate
	+		+		+		++	0	Treatment, failure. Deep-seated neurosis suspected
++	+++	++	++	+	+++	++	+++	Euphoria	"Effect of drug like that of 3 scotch and sodas"
	+++		+++		+++		+++	0	Symptoms recurred on omitting drug in early period of treatment
++	+++	++	+++	+	+++	++	+++	0	Slow improvement in muscle spasm
+++	+++	+++	+++	+++	+++	+++	+++	0	Drug added little to therapy
	++++		+++		++++		+++	Drowsiness	No response with 1.2 Gm. daily; quick control of spasm, 2.4 Gm.
++	++	+++	+++	++	+++	++	++	0	Significant tranquilizing effect only. *Died of rheumatic heart dis.*
+	+	+	+	0	+++	+	+	0	No effect on phantom pain
	+++		+++		++		++++	0	Spasm well controlled. No effect on phantom pain

TABLE

28 Cases of Central Nervous System Disturbances in Which (Cerebral Palsy, Spastic and Athetoid; Quadri- and Hemi-

No.	Patient	Sex	Age, yr.	Diagnosis and symptoms	Previous duration of conditions	Daily dose			Duration of therapy
						mg.	Sched.	Total Gm.	
Adult hemiplegia									
1	W.L.	M	34	Rt. hemiplegia after exc. brain tumor. Stiff, painful shoulder	3 mo.	800	t.i.d.	2.4	4 wk.
2	F.M.	M	53	Left hemiplegia	2 mo.	800	t.i.d.	2.4	2 mo.
						reduced to 400	t.i.d.	1.2	
3	C.W.	M	68	Rt. hemiplegia, stiffness rt. hand	3 yr.	400	t.i.d.	1.2	2 mo.
4	M.W.	M	57	Left hemiplegia. Spastic left arm and leg	15 mo.	400	t.i.d.	1.2	
						800	t.i.d.	2.4	
5	L.M.	M	50	Left hemiplegia. Signs of developing psychosis. Had 4 previous cerebral accidents. Depressed by mephenesin	3½ yr.	400	t.i.d.	1.2	3 wk.
6	J.McW.	M	54	Left hemiplegia, pain left shoulder, wrist. Mild spasticity, left arm, leg. No voluntary motion of hand	2 mo.	400	t.i.d.	1.2	2 mo.
7	H.T.	M	66	Left hemiplegia. Possible multiple sclerosis. Dizziness. Irritability. Poor proprioception	5 yr.	800	t.i.d.	1.2	3 wk.
8	R.C.	F	53	Rt. hemiplegia, hand severely spastic. Obese and extremely uncooperative		800	t.i.d.	2.4	6 wk.
9	J.L.	M	54	Degenerative disease of spinal cord. Tension, pain, contractures of rt. leg. Severe spastic paraplegia		400 changed to 800 optimal dose	t.i.d. h.s.	1.2	6 mo.
Cerebral palsy, athetoid									
10	J.S.	F	14	Cerebral palsy, tension athetosis, rt. hemiplegia, rt. hand seizures	Since birth	400	t.i.d.	1.2	
						400	q.i.d.	1.6	
11	B.O.	F	7	Cerebral palsy, severe tension athetosis	Since birth	200	t.i.d.	0.6	
						initially increased to 400	t.i.d.	1.2	6 mo.
12	D.G.	M	8	Cerebral palsy, severe tension athetosis. Woke 5–11 times a night	Since birth	200	t.i.d.	0.6	6 mo.
13	M.C.	F	13	Cerebral palsy, mod. tension athetosis. No speech. No self-help	Since birth	800	t.i.d.	2.4	2 mo.
14	C.B.	F	4	Cerebral palsy, moderate tension athetosis. Wide violent movements	Since birth	200	b.i.d.	0.4	1 mo.
15	N.S.	F	6	Cerebral palsy, severe tension athetosis. Severe torsion	Since birth	200 initially, then 800	t.i.d. h.s.	0.6 0.8	6 mo.

II
Meprobamate Was Used as Adjunct to Physiotherapy
plegia; Dystonia Musculorum; and Spinal Cord Disease)

Decrease in spasticity	Decrease in muscle tension	Decrease in involuntary movement	Response in performance	Relief of emotional tension	Side effects	Remarks
++	++	—	++++	++	Slight drowsiness	Daily stretching exercises continuing. Improved motivation
++	++	—	++	++	Drowsiness on larger dose only	Stretching easier. Walks faster. Better performance of all activities on meprobamate
+	+	—	+	0	0	More relaxation in leg; greater ease in walking. Slight relaxation of hand. Result good for chronicity of case
++	++	—	++	0	0 Drowsy on larger dose	Moderate relaxation on smaller dose. Relaxation improved on increased dose. Flattened affect. Increased alertness. Stretching easier. All activities better performed
0	0	—	0	0	0	No response
++	++	—	++	0	0	Some relaxation of spasm. Improvement in strength and range of motion
0	0	—	0	0	0	No response
+	+	—	+	+	0	Response apparently combination of reduced emotional tension and actual lessened spasticity. No improvement in personality or manageability
+++	—	—	+++	++	0	Much less spasticity. Knee straightened to within 10 degrees of full extension. Was able to walk with canes; later could take 5 steps without aid. *Died from progression of spinal cord disease*
—	++++	+++	+++	++	0	Excellent result. Tension much lessened. Hand completely relaxed. Seizures about half as severe, but frequency not reduced. No increase in drowsiness from diphenylhydantoin and phenobarbital. Tension recurred 2 days after stopping drug; back to original level in 1 wk. On resumption of meprobamate in increased dose, prompt restoration of improvement
—	++++	+++	++++	—	0	Dramatic change. Excellent relaxation. Began to talk. Was ready for speech but tension had prevented performance to capacity. Gained 15 lb. in 1st 4 mo.
—	+++	+	++	—	0	Moderate reduction in tension. Easier to brace. Requires less assistance in walking. Sleeps through night
—	+++	++	++	++	0	Parents' note after 2 months, "Tablets really have quieted her nerves"
—	+++	++	++	0	Slight drowsiness first week only	Mother reported less motion, better voice control, greater ease in handling and bracing. Requests continuation of medication
—	+++	+	+	0	Daytime drowsiness on t.i.d. No drowsiness on 1 dose h.s.	More easily braced. Cannot be held in chair without medication; easily restrained with medication. Best response on 1 dose at bedtime

Table 11 Continued on Page 460

TABLE

28 Cases of Central Nervous System Disturbances in Which (Cerebral Palsy, Spastic and Athetoid; Quadri- and Hemi-

No.	Patient	Sex	Age, yr.	Diagnosis and symptoms	Previous duration of conditions	Daily dose			Duration of therapy
						mg.	Sched.	Total Gm.	
16	H.K.	M	18	Cerebral palsy, moderate tension. Incoordination	Since birth	400 800	t.i.d. t.i.d.	1.2 2.4	1 wk. 1 mo.
17	E.C.	M	6	Cerebral palsy, severe tension athetosis	Since birth	200	t.i.d.	0.6	3 mo.
18	J.B.	M	9	Cerebral palsy, severe tension athetosis	Since birth	400	t.i.d.	1.2	1 mo.
19	B.S.	M	12	Cerebral palsy, severe tension athetosis	Since birth	400	t.i.d.	1.2	3 mo.
20	C.R.	M	6	Cerebral palsy, severe tension athetosis. Vomits frequently in response to any emotional stimulus	Since birth	400	t.i.d.	1.2	5 days
21	D.W.R.	M	31	Cerebral palsy, tension athetosis	Since birth	400	t.i.d.	1.2	8 wk.
Cerebral palsy, spastic, and traumatic spastic conditions									
22	C.L.	F	12	Cerebral palsy, spastic rt. arm and leg. Grand mal seizures. Learning ability deteriorating	Since birth	400	t.i.d.	1.2	2 wk.
23	T.S.	M	6	Cerebral palsy, severe spastic quadriplegia. Severe grand and petit mal seizures. No speech, no self-help. 20 myoclonic jerks a day. 2 grand mal seizures a mo. on diphenylhydantoin and phenobarbital	Since birth	200	t.i.d.	0.6	1 mo.
24	M.F.	F	30	Cerebral palsy, severe spasticity; scoliosis, radiculitis. Extremely irritable; emotional outbursts. Difficult problem in emotional and physical management	Since birth	400	t.i.d.	1.2	6 wk.
25	F.P.	M	9	Traumatic spastic quadriplegia, all extremities in flexion. Rt. leg fixed; contractures, tremors		200	t.i.d.	0.6	6 mo.
26	D.H.	M	11 mo.	Cerebral palsy, moderate spasticity. Microcephalic, retarded. Unable to sit	Since birth	400	t.i.d.	1.2	3 wk.
Dystonia musculorum deformans progressiva									
27	S.B.	F	16	Dystonia musculorum deformans progressiva. Severe tension, trunk flexion 90°. Fasciculation left quadriceps. Totally incapacitated without medication. Could walk 8 blocks unassisted with quinine sulfate, 30 gr. daily		400 800	t.i.d. t.i.d.	1.2 2.4	2 wk. 7 wk.
28	A.W.	F	13	Dystonia musculorum deformans progressiva	Since birth	400	t.i.d.	1.2	1 mo.

II (*Continued*)
Meprobamate Was Used as Adjunct to Physiotherapy
plegia; Dystonia Musculorum; and Spinal Cord Disease)

Decrease in spasticity	Decrease in muscle tension	Decrease in involuntary movement	Response in performance	Relief of emotional tension	Side effects	Remarks
—	+++	++	+++	++	Slight drowsiness 1st few days; none thereafter	No response to smaller dose. Improved on doubled dose. Better muscular control. "Knock-out" effect on combination with alcohol or chlorprophenpyridamine
--	++	+	++	—	0	Significant improvement. Medication continued
--	++	+	+	+	0	Significant improvement in ease of handling. Medication continued
--	++	+	+	—	0	Change not significant. Medication discontinued
--	0	0	0	0	Vomiting, somnolence	Vomited on second day. Taken off drug by mother
—	+++	++	+++	+++	0	Discontinued. Tension and nervousness increased. Spontaneous fracture from muscle tension and athetosis. Resumed drug. More data later
++	—	—	+++	+++	0	Seizures less severe, frequency unaffected. Alertness increased. Stopped drug because of mother's anxiety. Seizures increased. Resumed drug. Seizures lessened, improvement restored. Increased learning ability continued on meprobamate
++	—	—	—	—	0	Seizures less frequent and less severe. Spasticity moderately relieved. Diphenylhydantoin and phenobarbital continued
+	—	—	—	0	Slight drowsiness	Behavioral difficulties controlled on chlorpromazine. Relapsed on meprobamate. Chlorpromazine resumed, with restoration of earlier response
++	—	+++	+++	+	0	Less spasticity, contractures softer. Improvement more rapid with meprobamate. Cessation of tremors
0	—	—	0	—	Drowsiness	
0	0	0	0	0	0 0	Meprobamate substituted abruptly for quinine. Initially strength, weight, and endurance increased. Back relaxed enough for brace and patient assisted with family moving. At first better tension control with meprobamate than with quinine. After 7 wk. on this regimen, her condition regressed; dose of quinine was increased to 15 gr. and meprobamate was reduced to 1.2 Gm. daily. Control still was not attained, and quinine, 30 gr. daily, was resumed
—	0	0	0	0		No change

Most of the children less than 10 years of age received doses of 200 mg., usually administered three times a day. The dose was increased in some cases (table II).

In group 1, 1.2 Gm./day was sufficient for 76 per cent of the patients; 12 per cent required a total daily dose of 2.4 Gm.; 12 per cent received 1.6 Gm./day.

In group 2, 23 per cent required a total daily dose of 2.4 Gm.; for 53 per cent, 1.2 Gm./day was sufficient; the remainder received smaller total daily doses, with the exception of patient no. 10, who received 1.6 Gm. The largest daily dosage was administered to 3 of the adults with hemiplegia, the 16 year old girl with dystonia musculorum deformans progressiva, and a 13 year old and an 18 year old boy with athetoid cerebral palsy.

PHYSIATRIC MEASURES

Physical therapy, in the form of heat, massage, traction, exercise, and educational techniques designed to prevent or correct deformities and to stimulate or maintain function, was employed for all patients as required.

A home program was instituted as indicated. In instructing arthritic patients, emphasis was placed on the fact that although they could not expect cure or even arrest of their arthritis, the physiatric regimen would at least tend to diminish the crippling effects.[26]

RESULTS

Method of Evaluation. In grading the results, observations were made in each instance by the same physician and therapist who had treated the patient initially, and the response was evaluated as objectively as possible. Although electromyographic determinations are valuable, the clinical impression of an experienced therapist who is thoroughly familiar with the case is an even more reliable basis for accurate evaluation of a patient's progress.

In those suffering from musculoskeletal disorders (group 1), reduction of spasm was determined by palpation; measurements were taken of joint range, of ease and speed of motion, and of improvement in function, according to standard procedures.[27, 28] Relief of pain was estimated on the basis of the patient's reports and on the dosage of analgesic drugs required for comfort.

In patients with central nervous system lesions (group 2), spasm and muscle tonus were evaluated by palpation; the increased range of motion permitted by relaxation of the contractures was measured. Control of involuntary movements or tremors in the athetoid children was evaluated as objectively as possible by increase in performance or by ease of bracing. For those with adequate intellectual potentialities, learning capacity as well as physical achievement was compared with previous performance. All these children had been followed for several years, so that a reliable base line of progress had been established, and their previous course was used as a control.

Among the adult paralyzed patients, increased ability to perform the activities of daily living was determined by critical comparison with the premedication status.

For group 1, an evaluation of 4-plus was assigned if pain, spasm, and emotional tension were completely relieved and range of motion was as near normal as possible

in light of the patient's other limitations. Response was considered 3-plus if symptoms had been reduced and performance improved by more than half. A 2-plus evaluation indicated definite improvement, but with performance less than half the degree desired. A 1-plus result indicated a noticeable, although slight, amelioration of symptoms and improvement in function.

For group 2, a 4-plus, or excellent, response represented complete subsidence of muscle spasm, tonus, and emotional tension, with performance restored to normal or developed to the maximum possible in the condition of the patient. Response was considered 3-plus, or good, if performance increased more than 50 per cent; 2-plus, or fair, if performance increased less than 50 per cent; and 1-plus, or slight, if there was a small but noticeable improvement, such as a better reach and grasp. Many of the patients in both groups are still under treatment.

Clinical Response. Group 1. Of the 27 patients, 40 per cent (suffering from whiplash injuries, herniated intervertebral disc, and fibromyositis of neck and shoulders) had a 4-plus result. Almost all the others (54 per cent of the series) experienced a 3-plus or 2-plus result. The 2 most resistant cases, in which the result was only 1-plus, involved a 45 year old man (no. 19) with whiplash injury complicated by osteoarthritis and a 50 year old man (no. 26) with reflex dystrophy of shoulders after amputation of the forearms three years previously. The other amputee (no. 27), whose case was similar, had suffered his accident four months before the start of physical therapy, and meprobamate was included in the regimen from the beginning. This patient had a 3-plus result in the first month of treatment.

Phantom pains experienced by both amputees have not been influenced by the medication.

All patients in group 1, therefore, showed some progress in response to physical therapy, and in all, improvement was more satisfactory after meprobamate was added to the regimen. With reduction of nervous tension and alleviation of pain, analgesics were less frequently required; if needed, fewer and smaller doses, for shorter periods, sufficed. Hypnotics were rarely necessary.

In addition to lessening of the emotional tension, there was actual relaxation of the contracted muscles so that they yielded more readily to stretching and manipulation. In most cases the patients became more tractable and cooperated more willingly in carrying out the prescribed home exercise program. Thus their progress was more rapid and physical therapy could be terminated earlier.

Group 2. Seventy-six per cent of the group suffering from central nervous system disturbances showed some improvement after meprobamate was instituted as an adjunct to physical therapy. On a total daily dose of 1.2 Gm., spasticity was lessened in the affected local muscle groups in the adult hemiplegic patients, without excessive general muscular relaxation. Thus the desired movement of the paralyzed upper and lower extremities could be achieved with greater ease, but the patient did not become so relaxed as to lose interest in efforts toward improvement. Several in this group suffered the emotional problems characteristic of victims of cerebral involvement; however, with one exception, their nervous tension was better controlled on addition of meprobamate to the physiatric regimen.

In the treatment of hemiplegic patients, it is important to watch closely for psy-

chologic reactions. One elderly man became depressed and somnolent on the 1.2 Gm. daily dose, and signs of agitation appeared when the effects of the drug wore off.

The response of the group with cerebral palsy showed presumptive evidence of a regulatory effect on the central nervous mechanism. A very definite reduction of tension was observed in both spastic and athetoid patients, with perhaps a somewhat more pronounced effect in those with tension athetosis. In 8 patients particularly (no. 10 through no. 16 in the athetoid group and no. 25 in the spastic group), advancement progressed at a significantly more rapid rate than had occurred under other therapeutic management or without treatment.

Improvement usually became noticeable after about three days of medication, with perceptible muscular relaxation and lessening of flailing motions, so that braces could be more readily applied and the patients more easily handled. Relaxation in those who had formerly been capable of some voluntary motor activity enabled better muscular control and coordination and greater strength of movement. Thus, walking was accomplished with less difficulty and increased endurance; spastic upper extremities became less helpless, with development of some grasping ability in the hands in certain instances. Speech became somewhat more intelligible and voice control more natural. Although it has been reported that meprobamate is contraindicated in the presence of grand mal epilepsy, no increase in either frequency or severity of seizures was observed in this series. When the dosage was adjusted, there was no impairment of intellectual functions.

The change in these patients was attributed to both lessening of emotional tension and alteration of the neuromuscular mechanisms. There was usually a distinct improvement in disposition; the children became less irritable and began to gain weight at once. Constipation and vomiting (which is likely to occur frequently in athetoid patients because of hypermotility of the gastrointestinal tract) were less of a problem than formerly. Children who had wakened often at night (such as patient no. 12) slept soundly on the medication.

There were 7 failures (25 per cent) in group 2. One patient, a completely helpless and mentally retarded spastic, showed no effect of any kind. Another child, who had severe tension athetosis and vomited frequently in response to the slightest stimulus, vomited after two days of medication; his mother discontinued the drug. The third was a 30 year old cerebral spastic quadriplegic, a difficult problem in physical and behavioral management. Two were victims of a progressive degenerative disease, and 2 were hemiplegic patients, 1 being the elderly individual previously described, in whom undesirable psychologic reactions developed.

Two deaths occurred, both from causes unrelated to the medication. One, an arthritic in group 1, died of severe rheumatic heart disease. This patient had a 2-plus relaxation from the drug and was able to sleep without hypnotics for two to three hours at a time, which formerly had been impossible. The other death occurred in group 2. This patient, who was suffering from a progressive degenerative spinal cord disease, experienced definite relaxation of spasm and muscle tonus while on the medication.

Side Effects. Drowsiness, observed during the first week or 10 days of therapy, was the major side effect of medication. This was controlled by reducing the dose,

which in most cases could be increased later if desired. For example, patient no. 15 (table II), a 6 year old girl with severe tension athetosis, showed considerable drowsiness on 200 mg. three times a day. When the medication was increased to 800 mg., given in one dose at bedtime, she slept well at night, and by morning the sedative effects had worn off. Satisfactory relaxation, with reduction of involuntary motions, was maintained well throughout the entire 24 hours, so that she could be braced and held in a wheel chair during the day. The child is now attending school, and the mother feels that meprobamate is essential to her progress.

Two patients experienced an erythematous, itching rash on the hands that disappeared when medication was discontinued.

Patient no. 13, in group 1, a 42 year old woman with a possible neurosis, experienced a very satisfactory muscular relaxation and relief of her emotional tension while on the medication, but had headache and nausea when the drug was stopped. Spasm promptly recurred in the muscles about the shoulder, and the range of motion decreased abruptly. In this group, 2 patients with severe spasm of cervical musculature exhibited no response to a dosage of 400 mg. three times a day, but spasm subsided within 12 hours after the dose was increased to 800 mg. on the same schedule.

DISCUSSION

Meprobamate appears to influence both affect and neuromuscular control. The compound unquestionably tranquilizes the emotions and also appears to exert a direct physical relaxant action. Thus, in the muscle in spasm, tension and rigidity are released and tonus is lessened to an extent over and beyond the effect produced by mere reduction of emotional stress.

In general, the patients suffering acute muscle spasm showed the most encouraging response. When treated in an early stage, the irritable muscle is more promptly susceptible to measures designed to relax and elongate the contracted fibers. In the presence of an old contracture, the chief value of meprobamate lies in alleviation of anxiety and apprehension so that the patient will be able to tolerate the more vigorous stretching required. Psychosomatic symptoms were alleviated in this series in the majority of cases, and in 1 patient premenstrual tension was lessened. Meprobamate is now used in this clinic almost routinely as a supplement to physiatric treatment of the shoulder-hand syndrome, whiplash injuries, and acute low back disabilities.

In management of the patients with central nervous system lesions, success was less predictable than in the musculoskeletal cases, but when relaxation and improvement in performance occurred, the effect was maintained as long as medication continued. The compound has a definite usefulness in treatment of tension athetosis. In spasticity caused by cerebral damage, muscular relaxation was limited. In this group only did patients exhibit a tendency to adverse psychologic reactions.

The first detectable sign of increased muscular and emotional relaxation appeared in a few hours after start of medication in both the musculoskeletal disabilities and the central nervous system disturbances. The peak of effect was achieved in four days or less. No patient developed a tolerance to the drug, although medication was

prolonged in some cases as long as six months. Rarely was it necessary to increase the dose to support the initial results.

In chronic cases requiring long term management, all patients relapsed on cessation of the medication, usually in about two days.

CASE REPORTS

Patient no. 25 (table II), a boy with traumatic spastic quadriplegia, presented an especially serious case. All extremities were in flexion, with contractures and tremors. The right leg was fixed. Daily physical therapy was employed, resulting in slow but steady improvement. After three months, meprobamate was added, in doses of 600 mg. daily, with gratifying results in lessening of spasticity and complete cessation of tremor. It was possible to begin academic instruction shortly after medication with meprobamate was included in the treatment.

Dramatic change also was seen in patient no. 11, a 7 year old girl with severe tension athetosis. On a physiatric program, with meprobamate, relaxation was 4-plus, and during the six months of medication she began to talk. It was suspected that she may have been ready for speech before this time, but extreme tension prevented performance to the full extent of her capacity. This child gained 15 pounds in the first four months of treatment.

An additional case of special interest is that of patient no. 10 (table II). This 14 year old girl with athetoid cerebral palsy and right hemiplegia with grand mal seizures had no use of the entire right upper extremity. On addition of 1.2 Gm. meprobamate daily to the anticonvulsant medication she had been receiving, a 4-plus result was obtained. Muscular and emotional tension was greatly lessened, and athetoid movements were reduced. Her seizures were about half as severe but the frequency was not altered; drowsiness previously experienced from the anticonvulsants was not increased by addition of meprobamate. The hand became relaxed, and she learned to use it to about half the normal extent in dressing herself, eating, and craft activities. She began unconscious use of the hand in movements such as opening a door or stabilizing a jar for removal of the lid.

Two days after administration of meprobamate was stopped (but not the anticonvulsants), tension recurred and increased to the original level in one week. Meprobamate was then resumed in a larger total daily dosage—1.6 Gm.—with restoration of the former degree of relaxation.

SUMMARY

Meprobamate was used as an adjunct to the physiatric management of 55 patients for periods up to six months. Twenty-seven had musculoskeletal disabilities and 28 were suffering from neuromuscular disturbances resulting from pre- or paranatal damage to the central nervous system.

Initially, 800 mg. three times a day was recommended for adults. Later the dose was adjusted, if advisable, to 400 mg. on the same schedule. Children less than 10 years old usually received 200 mg. three times a day. However, 1 child with severe tension athetosis became drowsy on this dosage. Daytime somnolence was eliminated without interfering with the relaxant effects of the drug by administering a single dose of 800 mg. at bedtime.

In patients with musculoskeletal disorders, 1.2 Gm. daily sufficed for 76 per cent; 12 per cent required a total daily dose of 2.4 Gm.; 12 per cent received 1.6 Gm./day. Of the patients with central nervous system lesions, 23 per cent required a total daily dose of 2.4 Gm.; for 53 per cent 1.2 Gm./day was sufficient. The other patients received smaller total daily doses in most instances.

Musculoskeletal disorders treated in the early, acute stages responded most satisfactorily. In 40 per cent of this group, pain, spasm, and emotional tension were

completely relieved and range of motion was restored as nearly as possible to normal (4-plus result). In an additional 54 per cent, improvement was definitely increased over the response to physical therapy alone (3-plus or 2-plus result). The progress of all patients in this group was more satisfactory after meprobamate was added to the regimen, and physical therapy could be terminated earlier. Meprobamate is now used in this clinic almost routinely as a supplement to physiatric treatment of whiplash injuries, shoulder-hand syndrome, and acute low back disabilities.

Some degree of improvement was discernible in 76 per cent of the group with central nervous system lesions after addition of meprobamate to physical therapy. Those with cerebral palsy showed presumptive evidence of a regulatory effect on the central nervous mechanism, which was somewhat more pronounced in the group with tension athetosis. There was perceptible muscular relaxation with lessening of flailing movements in most, so that braces could be more readily applied and the patients more easily handled. In spasticity caused by cerebral damage, muscular relaxation was more limited.

The first signs of clinical response were detectable in a few hours, and the peak of effect was reached in four days or less. Relaxation continued throughout the period of treatment. Rarely was it necessary to increase the dose to support the initial results. All chronic patients who improved on the supplementary medication relapsed on cessation of the drug, usually in about two days. Generally there was a distinct improvement in disposition and, in the children, a tendency to gain weight.

Meprobamate appears to alter the neuromuscular mechanisms as well as to lessen psychic tension. Thus muscle tonus is reduced, and spasm and rigidity are released to a degree over and beyond the effect achieved by relief of emotional stress alone.

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Experimental Studies with PM 1090

PRELIMINARY REPORT

Robert M. Edwalds, M.D.

NORTHVILLE STATE HOSPITAL

NORTHVILLE, MICH.

PM 1090 is described by the manufacturers (Parke, Davis & Co.) as a potent analeptic agent acting primarily on the midbrain and the medulla. The effect is rapid in onset and long in duration. It is nearly equally effective by oral or by parenteral administration. It is a stimulant to the respiratory center and to the vasomotor mechanisms and is a very effective antagonist against central depression induced by phenobarbital and other central nervous system depressants.

PM 1090 is approximately five and one-half times more potent an analeptic agent than is Metrazol. The acute lethal dose of PM 1090 in rats, mice, and rabbits is two to four times its effective dose.

Since PM 1090 resembles Metrazol in its action and pharmacology, this study was undertaken to determine the central nervous system stimulant effects of the drug in 10 chronic, idle, regressed, psychotic female patients. Patients were started on 22.5 mg. of the drug per day, in the form of one 7.5 mg. capsule three times daily. This amounted to a dosage level of approximately 0.5 mg./Kg. for most patients.

Routine urinalyses and complete blood counts were done at weekly intervals during the experiment and for about two weeks after the experiment was discontinued. Thymol turbidity determinations were made while patients were taking the drug. Bromsulphalein determinations were made after completion of the experimental studies. Electroencephalograms were taken toward the end of the experimental period and usually a few days after the patient had a seizure. Dosage of the drug was increased in most patients 10 to 20 days after the onset of the experimental studies.

Case 1—Patient C., aged 24. Prior to the experiment, the patient was unkempt, idle, and occasionally disturbed. No change was noted during or after the experiment. No seizure occurred. The patient was maintained on a dose of 22.5 mg./day for a total of 27 days. Laboratory studies were within normal limits. Electroencephalogram showed a normal tracing with strong, fast activity.

Case 2—Patient N. T., aged 36. Prior to the experiment, the patient walked the ward all day long, was uncooperative, mumbled to herself, and did not participate in activities. During the experiment, she became more restless, slightly more cooperative, and occasionally spoke a word. She was otherwise unchanged. The patient had a seizure, with involuntary urination and crying out (but without clonic or tonic convulsion), four days after the dose was increased from 22.5 to 45 mg./day. She was then maintained on 22.5 mg./day and remained on medication for a total of 34 days. Laboratory studies were within normal limits. Electroencephalo-

PM 1090 was supplied through the courtesy of Parke, Davis & Co.

gram showed a tracing with bursts of slow waves, consistent with episodes of delirium. They were not properly convulsive in form, and they were decreased by alertness. In 11 minutes of recording these may have occupied 80 per cent of the recorded time. At this point the only guess was that they represented a withdrawal response.

Case 3—Patient B. R., aged 39. Prior to the experiment, the patient was idle and silly. She sat in the ward all day long and did not participate in activities. No change was noted during or after the experiment. A seizure occurred one day after the drug was increased from 22.5 to 45 mg./day. Involuntary urination, with convulsive movement and confusion, was noted. The patient was then maintained on a dose of 22.5 mg./day for a total of 29 days. Laboratory studies were within normal limits except for a Bromsulphalein reading of 12 per cent. Thymol turbidity was 1 unit. No clinical signs of illness were noted. Electroencephalogram four days postseizure showed a tracing with infrequent but definite paroxysms of convulsive form. There were no localizing signs.

Case 4—Patient S. P., aged 51. Prior to the experiment, the patient was unkempt, idle, inactive, and did not even make her own bed. She shuffled slowly about the halls, preoccupied and confused. An improved personal appearance (she wore make-up, and had her hair fixed) was maintained during and after the experiment, and she was more alert and talked coherently on occasion. The impression was slight to moderate improvement. Dosage of the drug was gradually increased from 22.5 to 90 mg./day. The patient had three seizures one day after the dose was raised to 90 mg., with convulsive movements, unconsciousness, confusion, and involuntary urination. The last seizure was terminated with intravenous Amytal. The patient was then maintained on 22.5 mg./day for 26 days. Laboratory studies were within normal limits. Electroencephalogram five days postseizure showed a tracing with bursts of several rhythms, convulsive in form. They were not localized and may have been associated with other episodal symptoms and seizures. This was the same pattern as was seen previously in this patient.

Case 5—Patient D. C., aged 32. Prior to the experiment, the patient was untidy, unkempt, cried, and would not feed herself. She would wet the bed if not taken to the bathroom, and she was idle and catatonic. No change was noted during or after the experiment. A seizure occurred one day after the dose was raised from 22.5 to 34 mg./day, with convulsion, involuntary urination, and unconsciousness. The drug was discontinued following the seizure. The patient was on the experimental drug for a total of 14 days; laboratory findings were within normal limits. The first electroencephalogram, one day postseizure, showed a tracing with an unusual distribution of the *repose* wave. There was no known clinical correlate of this pattern. There were no seizure discharges. The second electroencephalogram, four days postseizure, showed a tracing just like the previous record except that muscle tension was increased somewhat. It was unusual in distribution of the *repose* waves, but had no abnormal waves. In the third electroencephalogram, eight days postseizure, the repose activity shifted to the occipital areas for part of the recorded time; the cause of this was not apparent. A change of state was suspected since the rhythm was slower.

Case 6—Patient H. L., aged 50. Prior to the experiment, the patient was unkempt, idle, and picked at herself. Affect was very flat. She did not participate in any activities. No change was noted during or after the experiment. No seizure occurred. Dosage of the drug was gradually increased from 22.5 to a maintenance dose of 60 mg./day for a total of 33 days. Laboratory findings were within normal limits except for the Bromsulphalein reading of 7 per cent. Thymol turbidity was 3.5 units. No clinical signs of illness were noted. Electroencephalogram one day after the drug was discontinued showed no abnormality in six minutes of recording in an alert, uncooperative state.

Case 7—Patient J. G., aged 35. Prior to the experiment, the patient was unkempt, untidy, nervous, and idle. Flight of ideas and word salad were noted. Affect was flat, but the patient exhibited some anxiety. She was not participating in any activity. Shortly before the experimental studies were begun, visits from the patient's mother were restricted. The patient became more alert and ate better during the experiment. She dressed herself but her personal appearance was not markedly changed. She became more coherent and willing to talk, and she started going to occupational therapy, to movies, and to the beauty parlor. No change in affect was noted. The impression was moderate improvement. The patient had a seizure, with convulsion, unconsciousness, and involuntary urination, 23 days after the onset of the experiment. Dosage of the drug was then reduced from 22.5 to 15 mg./day. The patient was maintained on the experimental drug for a total of 28 days. Laboratory findings were within normal limits. Electroencephalogram four days postseizure showed a normal tracing in an unrelaxed subject.

Case 8—Patient E. T., aged 31. Prior to the experiment, the patient was very unkempt, combative, idle, markedly delusional, and out of contact with reality. She became less combative during the experiment, returning to a combative state after the experimental drug was discontinued. No other change was noted during or after the experiment. A seizure, with convulsion, unconsciousness, involuntary urination, and confusion, occurred two days after the dose was raised from 22.5 to 45 mg./day. The dose of the drug was then reduced to 22.5 mg./day. Another seizure occurred 10 days after the first seizure, with convulsion, unconsciousness, and lip biting. Nausea and restlessness were noted for as long as 24 hours preceding the seizures. The patient was then maintained on 15 mg./day, remaining on the experimental drug for a total of 30 days. Laboratory findings were within normal limits except for the Bromsulphalein reading of 7 per cent. Thymol turbidity was 1.5 units. No clinical signs of illness were noted aside from the temporary nausea and vomiting. Electroencephalogram three days after the second seizure showed a low voltage, arrhythmic pattern without sign of convulsive or organic disturbance. This pattern may have been, in part, the result of the alertness, as the subject was never truly reposed.

Case 9—Patient R. P., aged 32. Prior to the experiment, patient was fairly neat, but was sarcastic. She was idle on the ward. Paranoid delusions were present; affect was flat. No change was noted during or after the experiment. No seizure occurred. The patient was maintained on a dose of 22.5 mg./day for a total of 30 days. Laboratory findings were within normal limits. Electroencephalogram showed a normal tracing.

Case 10—Patient O. M., aged 29. Prior to the experiment, the patient was unkempt, uncooperative, and occasionally combative. She was idle on the ward. A silly smile and flat affect were noted. The patient became slightly more cooperative and ate better during the experiment. No other change was noted. The impression was slight improvement. Dosage of the drug was increased from 22.5 to 60 mg./day. The patient became tremulous and nauseated, and vomited at this level. The dose was then reduced to 30 mg./day. A seizure occurred at this level, with convulsion, unconsciousness, and confusion. The patient was then maintained on 15 mg./day, and she remained on the experimental drug for a total of 33 days. Laboratory findings were within normal limits. Electroencephalogram one day after the drug was discontinued showed no classical seizure discharges. There were rare bursts of slow waves in the frontal areas and a slight voltage reduction on the right side. These imply physiologic change and perhaps episodes of decreased frontal lobe function.

SUMMARY AND CONCLUSIONS

PM 1090 is a powerful analeptic drug, apparently safe for human use. Seven of the 10 patients who received PM 1090 had one or more grand mal seizures. Three of the 7 patients who had seizures showed some slight improvement in mental condition. The remaining 7 patients remained essentially unimproved. Except for nausea and restlessness occasionally preceding a seizure, no other toxic effects were noted. All patients took oral medication willingly, even following a seizure. Because of the drug's convulsant effects, it is not recommended as a stimulant for geriatric patients. No conclusions about therapeutic effects of this drug are possible at this stage of investigation. Further clinical studies seem indicated and are currently in progress.

THREE COUNTRIES JOIN W.H.O. Under the presidency of Professor Jacques Parisot, the Ninth World Health Assembly granted full membership in the World Health Organization to Morocco, Tunisia, and the Sudan, which had been associate members. Associate membership in the Organization was granted to the Gold Coast, the Federation of Nigeria, and Sierra Leone. This brings the total membership of the World Health Organization to 88.

RADIOACTIVE CARDIAC TRACERS. Charles F. Burke of the General Tire & Rubber Company announced the development of a new machine called the AGN 201 Nuclear Reactor that produces and stores radioisotopes that will be immediately available for the diagnosis of heart disease. The device activates a salt solution that is then injected into an arm vein; radiation counters on the anterior chest wall then trace the tagged blood.

PAY INCREASE FOR MILITARY MD'S. A bill increasing bonuses for physicians, sponsored by the Department of Defense to induce more physicians to make a career of military service, has been signed by President Eisenhower. Physicians in the armed services now receive a monthly bonus of $100 in addition to their regular military pay. Under the new legislation, the bonus would be increased to $150 a month after two years, $200 a month after six years, and $250 a month after 10 years.

TOTAL SYNTHESIS OF RESERPINE. Robert Burns Woodward, Professor of Chemistry at Harvard University and synthesizer of strychnine, cortisone, lysergic acid, and quinine, reported that the total synthesis of reserpine has been achieved less than a year after the chemical structure of the alkaloid was determined. Sixteen chemical steps were required to complete the synthesis.[1]

Q FEVER PREVENTIVE. Colonel William D. Tigertt and Lt. Colonel Abram S. Benenson, of Walter Reed Army Institute of Research, Washington, D. C., reported at a recent meeting of the Association of American Physicians that Q fever is prevented when oxytetracycline is given late in the incubation period.

ORAL POLIOMYELITIS PREVENTION. Dr. Joseph Stokes, Jr., University of Pennsylvania, and his colleagues reported the successful immunization of infants with orally administered poliomyelitis virus. Using the SM strain of type I and the TN strain of type II poliomyelitis virus, attenuated by serial passage in mice, the virus was administered in milk to 225 infants 35 to 84 days of age. Antibody titer rose to satisfactory levels and persisted for as long as 47 to 50 months.

AMERICAN HEART ASSOCIATION MEETS. The 32nd annual meeting and 29th annual scientific sessions of the American Heart Association will be held in Cincinnati, Ohio, beginning Oct. 27 and continuing through Oct. 31, 1956. Those wishing to present either papers or scientific exhibits can obtain application forms from the Medical Director, American Heart Association, 44 East 23rd Street, New York 10, N. Y.

MEDICAL WOMEN'S INTERNATIONAL TOUR. An international tour is being arranged in conjunction with the Medical Women's International Association Council Meeting, which will be held in Burgenstock, Switzerland, from Sept. 21 to 24, 1956. The tour, beginning on Aug. 31, 1956, will include the Scandinavian countries, Western Germany, Switzerland, Alsace-Lorraine, and Luxembourg. Details may be obtained from Ada Chree Reid, M.D., M.W.I.A., 118 Riverside Drive, New York 24, N. Y.

RELIEF FOR NASAL ALLERGY. A group of South American physicians have found that the drug carbinoxamine maleate (marketed by McNeil Laboratories as Clistin Maleate) produces good to excellent results in over 85 per cent of perennial allergic rhinitis sufferers. Clinical studies, conducted at the National Institute of Allergic Diseases in Buenos Aires, included 94 patients suffering from a variety of allergic complaints to whom the drug was administered orally.[2]

INTERNATIONAL SYMPOSIA. Three monographs have been issued by MD Publications, Inc., New York, comprising the complete events and texts of recent international symposia. The subjects are "Health and Travel," "Medical Writing," and "Psychiatry and Religion," and all books are artistically bound and illustrated.

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Dr. Félix Martí-Ibáñez Appointed Professor of History of Medicine and Director of New Department by New York Medical College

New York Medical College, Flower and Fifth Avenue Hospitals, has appointed Félix Martí-Ibáñez, M.D., director of their History of Medicine Department, which was recently founded. He will also serve as Professor of the History of Medicine.

Dr. Martí-Ibáñez, a writer and medical historian, is the Associate Editor of ANTIBIOTIC MEDICINE & CLINICAL THERAPY, International Editor of ANTIBIOTICS & CHEMOTHERAPY, Editor of the INTERNATIONAL RECORD OF MEDICINE, and International Editor of the JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY.

Born in Cartagena, Spain, Dr. Martí-Ibáñez studied at the Medical School of the University of Barcelona and received his Doctorate in Medicine from the University of Madrid. Until 1939, he practiced psychiatry in Barcelona and taught medical history. He also edited several medical and literary journals and published two novels and several books on the history of medicine, psychology, and eugenics.

In 1937 Dr. Martí-Ibáñez was appointed General Director of Public Health and Social Service of Catalonia, and later became Under-Secretary of Public Health and Social Service in the Spanish Government. He officially represented Spain at the World Peace Congresses held in Geneva, New York, and Mexico City. He was wounded while serving as a major in the Medical Corps of the Spanish Air Force.

After his arrival in the United States in 1939, Dr. Martí-Ibáñez held positions as Medical Director with three leading pharmaceutical concerns. He also lectured in many Latin American universities and was made an honorary member of fifteen medical, historical, and psychiatric associations.

He participated in the International Congresses of History of Medicine, History of Science, Psychology, and Psychiatry held since 1950 in Amsterdam, Paris, Stockholm, Nice, and Rome, and he has published many papers on psychiatric and medical-historical subjects in American and European medical journals.

A Fellowship was awarded to Dr. Martí-Ibáñez by the American Medical Writers' Association at their annual meeting last year. Also, he was recently honored, by unanimous decision of the National Academy of Sciences of Cuba and by decree of the Government of Cuba, with the Order of Carlos J. Finlay in recognition of his scientific and educational work in medicine. He is a member of the Foreign Press Association and the Stage and Screen Foreign Press Club and contributes columns to Latin American newspapers. Articles and short stories by Dr. Martí-Ibáñez have appeared in *Esquire*, *Town and Country*, *Gentry*, *Art & Architecture*, and fantasy story magazines.

The Perennial Sneeze

The dismal season of pollinosis is once more upon us. Millions of allergic human beings are again doomed to their perennial cycle of mucosal congestion, dyspnea, and that tragi-ludicrous respiratory reflex called sneezing. It is sad to note that the attitude of the nonallergic person to sneezers is frequently along the lines of the Duchess' ruthless view in *Alice in Wonderland:*

> Speak roughly to your little boy
> And beat him when he sneezes,
> He only does it to annoy
> Because he knows it teases.

The medical profession has fortunately developed a more sympathetic view toward the sneeze-harried patient. Yet it is interesting to note that although the problem of allergic rhinitis must be as old as the human nose, medical attention was not directed to it until about 100 years ago. Previous to that, laymen had already associated seasonal sneezing with mowing and called their discomfort "hay fever" or "hay asthma," thereby initiating a libel on hay that persists to this day.

In 1835, we find that eloquent English writer and divine, Sydney Smith, writing to a Dr. Holland: "Light, dust, contradiction, an absurd remark, the sight of a Dissenter—anything, sets me sneezing." His reference to "contradiction" and "Dissenters" as possible etiologic sources of rhinitis anticipated what we now know about the possible psychoemotional component of allergies. The first medical reference to the annual allergy appears to be Dr. John Bostock's description of its symptoms in England in 1819 under the title of "A Case of Periodical Affection of the Eyes and Chest." In this country, the first notice of hay fever in a medical work seems to have been in Dr. J. A. Swett's *Treatise on Diseases of the Chest*, published in New York in 1852. The first scientific test on the disease was not done until 1873, when Charles H. Blackley of Manchester proved conclusively that the pollen of several plants, notably the grasses and cereals, was the culprit in seasonal catarrh.

When it comes to treatment, the words of Dr. Elias J. Marsh in New Jersey in 1877 are particularly apt: "Most sufferers from the disease have gone through a long list of medicines, one after another, with little benefit, but yet they look hopefully and eagerly for every new suggestion. Quinine, iron, arsenic, ammonia, camphor and carbolic acid,—each has had its advocate,—and still the disease makes its annual visitations and goes on with unimpeded progress." Among other remedies favored were the hypodermic injection of morphine, cold water, and simple cerate for the eyes and nose, Espic's cigarettes for the cough, and chloroform for the asthma.

We have today passed from the realm of opiates to that of antihistaminics and steroids. In the first group, it is now known that no one antihistaminic yields the best results in all patients. The most practical method so far devised is to divide

the drugs into four classes, based on their molecular structure. The structural formula seen in almost all the antihistaminics is $R\text{-}CH_2CH_2N(CH_3)_2$, the R representing any large radical. The dimethylamino portion $N(CH_3)_2$ appears to be the most active in blocking histamine. The drugs thus differ according to whether the R radical is linked to the dimethylamino radical by an oxygen, a nitrogen, or a carbon atom. To these are added a miscellaneous group of compounds such as chlorcyclizine and antazoline.

Treatment of hay fever with these drugs brings relief in a large proportion of cases, though always with the danger that sensitization may spread to other tissues to produce asthma or other allergic reactions. The use of specific pollen antigen, either alone or in combination with an antihistaminic, continues to give satisfactory results in many cases, particularly in patients who can be followed regularly over a number of pollen seasons; relief is hardly ever obtained after the onset of symptoms.

The use of steroids is a more debatable question. The literature abounds with reports of attempted treatment of hay fever with cortisone, ACTH, and allied compounds. In an editorial in the authoritative *Journal of Allergy* in 1953,[1] it was advised that adrenal corticosteroids could be used in seasonal allergies, providing precautions were taken as to dosage, and the patient's general reactions most carefully observed to obviate the side effects associated with adrenocortical dysfunction.

From the voluminous data on the treatment of allergies, one fact emerges: the problem is still largely in the realm of trial-by-error. We now know a good deal about the action of histamine, and we have become quite expert in the manufacture of antihistaminics. But the basic question remains of whether it is advisable to interfere with an allergy insofar as this is a natural reaction of the organism to an invading substance. By suppressing the reaction, may we not be interfering with the natural defenses of human tissues at the cellular and intracellular level, thereby weakening these elements in their efforts to survive, and possibly exposing them to other cytochemical dangers? As Dr. Marsh wrote some 80 years ago: "Perhaps nature, who caused the idiosyncrasy, may remove it; but her ways are inscrutable . . ." This is cold comfort for the sneeze-ridden patient, though possibly less bleak than the danger of self-medication with a constantly changing pharmacopoeia.

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GENERAL PRACTICE CLINICS

This section of General Practice Clinics features reports on papers delivered at current medical meetings in the United States and abroad.

Adrenal Hypofunction and Adrenalectomy in Human Diabetes

Presented by IRVING GRAEF, M.D., (New York University Medical School) before the New York Diabetes Association, October 27, 1955.

The role of the adrenal gland in carbohydrate metabolism is under constant study, although no precise role has as yet been assigned to it. There is a possibility of the involvement of glucocorticoids via gluconeogenesis. We have as yet no evidence that implicates the adrenal steroids in clinical diabetes mellitus. Addison's disease may precede, follow, or occur simultaneously with diabetes. A patient having both Addison's disease and diabetes may continue to have diabetes even after destruction or atrophy of the adrenal glands. These are mysteries of endocrine disharmony.

The development of a decreased insulin requirement in a diabetic patient requires investigation to see if perhaps Addison's disease is developing. Neoplasms of the pituitary or adrenal cortex are conditions in which diabetes can be worsened. The hormonal relationships during and after pregnancy should be investigated to determine if diabetes can be initiated here.

Certain types of diabetes involve more than a lack of insulin; e.g., the diabetes associated with the following: Kimmelstiel-Wilson's disease, splanchnic or peripheral arteriolar sclerosis, cardiac failure, arteriosclerosis with renal insufficiency, glomerular nephrosclerosis. Retinopathy is seen in such cases of malignant vascular diabetes.

Treatment of Spontaneous Pneumothorax

Presented by DR. ARMAND A. LEFEMINE, DR. EDWARD T. O'HARA, AND DR. JOSEPH P. LYNCH (Veterans Administration Hospital, Boston) before the Ninth Annual American Medical Association Clinical Meeting, Scientific Lectures, Boston, December 1, 1955.

The therapy of spontaneous pneumothorax should be individualized. The classical approach consists of bed rest and aspiration (thoracentesis) when necessary. The results with this method are good.

The closed thoracotomy method is being used, when indicated, early in the treatment of spontaneous pneumothorax at the Veterans Administration Hospital with the intention of decreasing morbidity, shortening convalescence, and decreasing chronic pneumothorax. Most authors report an average time for complete re-expansion of the lung treated by the classical method to be four weeks. With the closed thoracotomy, re-expansion occurs in a few minutes to a day. In patients

treated with closed thoracotomy there is a significant reduction in the time for expansion of the lung. The average time for complete re-expansion of the lung in the group treated by closed thoracotomy was 3.5 days as compared to 15 days for the remainder. One can determine the need for a closed thoracotomy in 24 hours. Closed thoracotomy should be used early when indicated by symptoms, collapse greater than 30 per cent, or lack of response to aspiration.

There was one complication in this series. One patient developed a persistent leak and formed a localized empyema. A small percentage will have recurrent collapse. To date, this has not happened in our series. When patients have recurrent collapse, thoracoscopy and the introduction of a sclerosing substance to adhere the parietal and somatic pleura should be considered. This procedure is not indicated in the routine case.

Newer Concepts of Arthritis

Presented by MORRIS ZIFF, M.D., before the New York Society of Physical Medicine and Rehabilitation, January 4, 1956.

Rheumatoid arthritis is a diffuse inflammatory disease of connective tissue with deposition of fibrinoid material. It overlaps the various other collagen diseases. For example, 25 per cent of cases of rheumatoid arthritis present arteritis. Of all the collagen diseases, it is most closely related to systemic lupus erythematosus.

The work of Stecher has shown a strong familial tendency for this disease. It is five times more common among siblings than it is in the rest of the random population.

In 1941 Sabin noted that 30 to 40 per cent of patients had a positive culture for pleuropneumonia organisms. The evidence for a direct connection of infection with rheumatoid arthritis, however, is yet to be proved. Lately, a rheumatoid arthritic-like disease has been reported in swine. It resembles that of man, clinically, pathologically, and by roentgenogram. It is caused by infection with a specific large bacillus, *Erysipelothrix rhusiopathiae*, resulting in a chronic, sterile polyarthritis, and eventually in ankylosis. Sensitization similar to that seen in swine may play an important role.

Emotional factors seem to play a role, but evaluation of this is almost impossible, because controls cannot be used. No clear evidence is available to show an absolute relation between stress and rheumatoid arthritis. Intact nervous innervation seems to be essential for the progression of the inflammatory process.

Abnormal serum proteins, as seen in persons with chronic, false positive Wassermann reactions, seem to be related to rheumatoid arthritis. Of more than a hundred people followed by Moore who were chronic, false biologic reactors, about 12 per cent eventually developed lupus erythematosus; 36 per cent, probable lupus erythematosus; and about 7 per cent, rheumatoid arthritis. Five per cent of patients with rheumatoid arthritis and 20 per cent with lupus erythematosus have false positive Wassermann reactions.

The sensitized sheep cell factor seems to be almost specific for rheumatoid arthritis. Ninety-two per cent of adult rheumatoid arthritics have a positive sensitized sheep cell agglutination factor, and 2 per cent of controls give false positive reactions.

This factor appears early in the course of the disease and has been detected as early as within the first three weeks after onset. In a series of patients having this factor, it was found in 10 of 11 with rheumatoid arthritis of less than six months' duration; 11 of 16 with juvenile arthritis; 1 of 11 with Marie-Strümpell ankylosing spondylitis; 0 of 9 with psoriatic arthritis; 0 of 9 with venereal arthritis or Reiter's syndrome; and 7 of 17 with systemic lupus erythematosus. These data would seem to indicate that diseases such as Marie-Strümpell disease, although pathologically the same as rheumatoid arthritis, may be different diseases. Further, it would seem that the sensitized sheep cell agglutinating factor is not simply a nonspecific by-product of inflammation. The repeated remissions and exacerbations in rheumatoid arthritis may be due to continued abnormal repeated stress of an antigen-antibody reaction.

Physical Medicine and Rehabilitation Aspects in the Treatment of Arthritis

Presented by EMMANUEL RUDD, M.D., before the New York Society of Physical Medicine and Rehabilitation, January 4, 1956.

Often fear is what brings the arthritic patient to the clinic, fear of physical crippling and loss of economic independence, of future wheel chair existence.

A correct diagnosis is of utmost importance. Some patients complain of pain and stiffness around joints and are suffering from "nonarticular rheumatism." They can be relieved by simple methods, and they need reassurance as to their future. Patients with degenerative joint disease must be told about the benign nature of their symptoms and the relative unimportance of Heberden's nodes, and should be shown the simple exercises to improve posture and muscle tone.

Rehabilitation of patients with rheumatoid arthritis must start the moment the diagnosis is made; education of the patient must teach him the nature and variable course of his illness. He should be told that no specific treatment exists, and that we speak of management and not cure of rheumatoid arthritis. Only from 15 to 25 per cent become severely disabled. With proper individualized management, the majority of patients can be made to live without major disability. The patient's family should be involved in the total care. Group discussion with several patients who have rheumatoid arthritis proves helpful.

Rheumatoid arthritics are usually treated on an ambulatory basis. Physical therapy should be used at home, and should be directed toward the prevention of deformities. The greatest cause of disability is flexion deformity of the knee and frozen shoulder. Exercises to build up the quadriceps muscles must be done twice a day, on arising and on retiring—the easiest is straight leg raising. When getting up from a chair, the patient should practice quadriceps tightening. Shoulders should be put through the full range of motion several times daily. This can be associated with daily activity, such as dressing and undressing. Other joints should also be put through the full range of motion at least once a day. Proper position of joints is important; for example, hands must be kept flat and extended and not flexed in the lap when at rest. The best heat measure at home is a warm bath daily.

Rheumatoid arthritics are hospitalized for short periods because of severe disease

activity. The balance between rest and activity should be carefully prescribed. Underwater exercises in a pool or tank are most helpful. The exercise program can be carried out only after there is reasonably good control of disease activity and pain.

Total care of rheumatoid arthritis has been greatly facilitated by various services instituted and encouraged by the Arthritis and Rheumatism Foundation. There is more active social service counseling, a back-to-work program, and a direct help program providing a housekeeping service and self-help devices when indicated.

Visualization of the Intracardiac Structures with Carbon Dioxide

Presented by THOMAS DURANT, M.D., (Temple University) before the Gerrish Milliken Lecture of the Graduate School of the University of Pennsylvania, Philadelphia, December 15, 1955.

Since carbon dioxide is 20 times as soluble as oxygen, large doses, as much as 7.5 ml./Kg. of body weight, can be injected rapidly into the circulation of animals without any serious effect. In the dog placed with the left side down, air injected causes a marked decrease of blood pressure and, in one third of the animals, death. When carbon dioxide is injected, there is no effect on respiration or blood pressure and there have been no deaths. When the animal is on its back, only one third live with air, and when the animal is on its right side, none of them live after the injection of much air. However, when carbon dioxide has been injected in any position, there has never been a fatality. While the left side down position is best for survival after air injection, the right side down position is best for minimal physiologic effects after carbon dioxide injection. This is because the carbon dioxide enters the lungs rapidly and is rapidly dissipated. It remains in the heart just long enough for one to see the internal structure. The tricuspid valve, pulmonary valve, pulmonary artery, right auricle, right ventricle, and even the trabeculae of the inside of the heart may be easily seen. When the carbon dioxide is injected through a catheter into the left ventricle, visualization of the left side of the heart is just as clear.

Further work in this field has yet to be done. First must be determined the smallest amount of carbon dioxide that can be injected into the antecubital vein and still give good visualization. The evidence to date indicates that less than 2 ml./Kg. can be used successfully. Second, this technique should be useful in the study of peripheral vascular disease, for, by injection of the gas into various arteries, the peripheral vascular circulatory situation might be determined.

Supersensitivity of the Isolated Cortex

Presented by FRANCIS A. ECHLIN, M.D., before the New York Neurological Society and Section of Neurology and Psychiatry, January 10, 1956.

We have studied the effects of surgical isolation and partial isolation of various parts of the cerebral cortex and the sensitivity of these parts to discharge, as measured

by the electrocorticogram. We found that the isolated cortex was more sensitive to stimuli, such as acetylcholine, Metrazol, and eserine.

Monkeys were prepared by encircling one area of the cortex with a subpial surgical incision, leaving the blood supply intact. Electrodes placed on the isolated cortex revealed an increased sensitivity to discharge. We feel that the supersensitivity of the isolated cortex is due not to injury but rather to the isolation per se. This is really an application of Cannon's law of supersensitivity after de-enervation. It is known that the area of cortex around a tumor is supersensitive and frequently gives rise to seizures. The destroyed tissue itself cannot cause a seizure. What happens is that the isolation produced by the tumor causes supersensitivity in the areas that it isolates. This supersensitivity may be a factor in the cause of focal cortical epilepsy. Another interesting speculation is that the clinical effects of lobotomy are in part due to a change in the physiologic chemistry (a supersensitivity) of the areas of brain isolated or partially isolated.

Open Heart Surgery under Hypothermia

Presented by DR. O. C. JULIAN, DR. W. S. DYE, DR. M. SADOVE, DR. W. GROVE, AND DR. H. COEHLO, before the Chicago Surgical Society, January 5, 1956.

Dr. Julian reported 12 cases in which open heart surgery under hypothermia anesthesia was utilized. These cases included pulmonary stenosis, infundibular stenosis, aortic stenosis, and closure of septal defects at the atrial level. Body temperature in these cases was depressed in a range of 25 to 30 C. Just prior to opening the heart, the incoming circulation is blocked by compressing the inferior and superior venae cavae. This trapping of the circulation has varied in length from three and one-half to nine and one-half minutes. In all the cases except those with an atrial septal defect, exposure was through a median sternotomy incision. There were 2 deaths in the reported series of 12 cases, which represents a mortality rate of 17 per cent. Dr. Julian expressed the opinion that the heart-lung preparation will replace this form of open heart surgery in the treatment of such conditions as tetralogy of Fallot and interventricular septal defects. Open heart surgery of this type will remain useful in the surgical correction of pulmonary and aortic stenosis and in the repair of interauricular septal defects.

Technical Aspects and Results of Studies on Herpes Simplex, ARD (APC), Vaccinia, Fowlpox, and Influenza Viruses

Presented by COUNCILMAN MORGAN, M.D., (Columbia University College of Physicians and Surgeons) before the Combined Meeting of the New York Society of Electron Microscopists and the New York Academy of Medicine, Section on Microbiology, January 12, 1956.

The electron microscope was used in studies on herpes simplex, ARD, vaccinia, fowlpox, and influenza viruses. The microscope works with electrons and magnetic lenses; the image appears on a screen and must be photographed. The chief ad-

vantage is the increased resolution. There are several disadvantages: The field is very small. A one-quarter inch specimen magnified 300,000 times equals 1.2 miles of area. When magnified 100,000 times, it equals 0.4 mile. It works in a vacuum. Electrons cannot penetrate thick sections; therefore, special microtomes are needed to cut sections of approximately 300 Å. There is a lack of superimposition; only a thin plane can be visualized. The sections must be very small in area.

In these studies, the specimens were fixed in osmium tetroxide, dehydrated, embedded in plastic, and then sectioned. On chorioallantoic membranes, it was seen that the influenza virus develops on the cell surface. The virus appears as spheres and rods. The vaccinia and fowlpox viruses develop within the cytoplasm. Herpes simplex virus particles are about 50 to 60 mμ. in size and develop in the nucleus. ARD virus particles (in HeLa cells) are about 50 to 60 mμ. and show a crystalline arrangement. They appear in the nucleus. The nuclear membrane breaks down, and the virus is released into the cytoplasm.

APC Viruses in Respiratory Disease—Clinical Aspects

Presented by DR. ROBERT H. PARROTT (National Microbiological Institute, Bethesda, Maryland) before the American Laryngological, Rhinological and Otological Society, Eastern Section Meeting, Boston, January 13, 1956.

In 1952 and 1953, tonsillar and adenoidal tissue was collected from children at the Washington Children's Hospital at the time of tonsillectomy and adenoidectomy. The original idea was to use this tissue as a basis for tissue culture work with viruses of the upper respiratory tract. It was hoped to study the changes in the tissue when inoculated with viruses. Surprisingly, more than 50 per cent of the material was already infected when the tissue was cultured. The viruses cultured and isolated in this manner became known as adenoidal-pharyngeal-conjunctival (APC) viruses. This name was applied because the pharynx, conjunctiva, and adenoids are the major source of these viruses in human beings.

The APC viruses are nonpathologic for animals, but can be grown in tissue cultures of human cervical carcinoma, monkey kidney, and human embryo fibroblast cells. They are heat labile, filterable, ether resistant, and antibiotic resistant. Immunologically the viruses have a common complement-fixing antigen. Based on neutralization tests, there are 6 to 10 immunologically distinct types isolated at present. Accumulative neutralization tests show that by adult life almost 100 per cent of the population has been infected with at least one of the viruses in the group.

Type 3 has been the most thoroughly studied of the group in so far as clinical disease is concerned. It has been shown that when the virus is associated with disease in man, there is a distinct antibody response. The virus can be recovered at the site of the pathology. It is not found in well persons. The virus is isolated only during the acute stage of the infection, not before or after, and is associated with a particular illness. Recently, inoculation into human beings has reproduced the illness. First attempts to inoculate the virus into the human pharynx failed. However, the disease has been reproduced by inoculating the virus into the con-

junctiva. The illness produced by the virus is called pharyngoconjunctival fever. A study of an outbreak of this disease was made on a hospital ward, with a total of 8 cases (type 3). The symptomatology of the pharyngoconjunctival fever (PC fever) is as follows: pharyngitis, rhinitis, fever lasting five to six days, cervical adenitis, conjunctivitis. At first there is a slight increase in the white blood count, which later falls.

The disease occurs in epidemics and sporadically. All ages and both sexes become infected; however, children are involved most. The highest attack rate in adults was found among mothers. PC fever is probably spread by direct contact with pharyngeal excretions. There is a very high attack rate. In a day camp outbreak studied, the attack rate was 72 per cent in the age group 4 to 7 years. Immunity increases with age; there is apparently no carrier state. Swimming pools may be involved in the spread. The incubation period is five to six days, and the communicability period is up to nine days. Type 3 virus was never isolated from tonsil tissue in the metropolitan District of Columbia area until a widespread epidemic occurred. The next year the virus was isolated on several occasions.

Antibiotics have no effect during the acute stage, but they may be helpful in treating secondary bacterial complications. Otitis media has been a problem in PC fever with nasal obstruction. This appears to occur more frequently in the winter months. Immunization may be possible. A vaccine has been produced that will protect the immunized person against a challenge dose of the virus. The present knowledge of the immunity that an attack confers is scant. There is apparently no cross immunity between types. A study of type 3 indicated that good immunity occurred after the attack, but the duration of this immunity is unknown.

Steroidal Hormones in Therapy of Breast Carcinoma

Presented by DANIEL LASZLO, M.D., (Montefiore Hospital, New York, New York) before the New York Roentgen Society, January 16, 1956.

The hormonal dependence and responsiveness of breast carcinoma can well be gauged by studies on calcium metabolism. The interest in such studies is also stimulated by the frequency of bone metastases in breast cancer and the major complications deriving therefrom. While roentgenograms elicit the presence of these lesions in the skeleton, studies on calcium metabolism offer additional supplementary information on the activity and growth rate of these skeletal metastases. In rapidly progressing tumors, for instance, marked elevation of urinary excretion, negative calcium balances, and hypercalcemia with its toxic manifestations are frequently observed.

The responsiveness of breast cancer patients to steroid hormone therapy can be well studied chemically by measuring urinary calcium, serum calcium, alkaline phosphatase, and the responsiveness of these patients to a calcium tolerance test that was developed in this laboratory.

Charts were shown that illustrated the metabolic improvement that followed palliative therapy such as castration and even preceded clinical improvement. The beneficial effects of stilbestrol and of testosterone on urinary calcium, calcium bal-

ances, and the calcium tolerance test were also illustrated by several examples. The dependence of some breast cancers on estrogens or androgens, the stimulation of malignant growth by these hormones as judged by their effects on calcium metabolism, and occasional development of hypercalcemia were described and illustrated by case histories and metabolic studies.

The beneficial effects of steroid hormones are due not only to the inhibition of tumor growth but also to the anabolic effects of these hormones on normal tissues and normal bone. For instance, the effects of steroid hormones on osteoporosis are well known, and many of the breast cancer patients suffer from osteoporosis due to immobilization as well as from the effects of the malignant growth. Therefore, studies of calcium metabolism offer an important guide for the evaluation of the state and progression of tumor and of the effectiveness of steroid therapy thereon.

Reconstruction of the Esophagus with Small Intestine in Cases of Lye Stricture

Presented by THOMAS G. BAFFES, M.D., before the Chicago Pediatric Society, The Children's Memorial Hospital, Chicago, January 17, 1956.

As a general principle in reconstructing the esophagus, whether in congenital atresia, accidental lye stricture, or any other disruption in esophageal continuity, one should use whatever remnants of the esophagus are available, even if periodic dilatation is necessary postoperatively. Only when adequate esophageal remnants are not available should the stomach or intestine be used for reconstruction. Using the stomach is not always feasible in pediatric cases because placing the stomach in the chest may dangerously limit the lung expansion. In such cases, a segment of jejunum can be isolated by a Roux-Y type of anastomosis brought up to the neck through the anterior or posterior mediastinum to be sutured to the proximal stump of the esophagus. Continuity is thus established with the small intestine. The blood supply of the isolated jejunal loop is carried up in the mesentery. Roentgenograms will show the gut coiled in the mediastinum. Dangers of this technique are that high acidity remains in the stomach without neutralization because the stomach is bypassed by the jejunal loop. Peptic ulceration with hemorrhage has been reported in such cases. However, this complication is rare, and the technique is quite satisfactory for establishing esophageal continuity.

Low Phosphatase Rickets

Presented by HARVEY WHITE, M.D., before the Chicago Pediatric Society, The Children's Memorial Hospital, Chicago, January 17, 1956.

Cases of vitamin deficiency rickets are rare today. In the presence of clinical rickets and if the vitamin intake is normal, then one must look for other causes. Of 8 cases of low phosphatase rickets described in the literature, 4 died in infancy. The various therapies tried included thyroid and growth hormone and high doses of vitamin D, none of which were successful. Prognosis depends on age; the younger the patient, the worse the prognosis. If there are renal lesions, the prognosis is

poor. The role of alkaline phosphatase in the body is controversial. It is believed necessary for ossification, and its role is in maturation of the protein matrix. In low phosphatase rickets, there is usually a hereditary factor. In 1 case, both parents had low phosphatase levels. In the differential diagnosis of low phosphatase rickets, one should consider osteogenesis imperfecta and chondrodysplasia.

The case presented is that of an infant with classical roentgen signs of rickets with normal calcium and phosphorus values. The alkaline phosphatase was very low. The patient died, and autopsy confirmed the presence of rickets.

Nocturnal Tingling

Presented by DR. JAMES W. STEPHENS (Associate Professor of Neurology) before the University of Colorado School of Medicine Postgraduate Course, General Practice Review, Denver, January 16–21, 1956.

Nocturnal tingling and burning in one or both hands is a frequent symptom that occurs more often among women than men. Pregnancy and the menopause are two periods when it seems especially prevalent. The incidence is strictly nocturnal; the course is long, benign, and self-limited; and there is a total absence of any physical signs. A characteristic episode follows somewhat this pattern: the patient wakens in the later part of the night with paresthesia of all the fingers of one hand; she sits on the side of the bed, rubs the flexor surface, walks around a bit, and returns to bed and to sleep until again awakened by a similar episode in the early morning. The following day the fingers will be swollen and stiff for about an hour; then she will be symptom-free until or unless she tries to knit or sew, when she will note awkwardness. This early morning stiffness and clumsiness may be accompanied by pain in the forearm and shoulder. The symptom (tingling) may be an extremely acute and distressing one. The total absence of physical signs has been mentioned, but if the condition is of long duration, a little wasting may be noted in the short abductor of the thumb.

The syndrome has been known for at least 60 years and has been attributed to many causes, such as the food restrictions imposed in England during and after World War II. Vitamin B therapy was of no value. Compression of the median nerve is of etiologic significance, and the syndrome has been found associated with acromegaly, arthritis, tuberculous tenosynovitis, and similar conditions. Various types of therapy have been tried in the past, ranging from surgery to psychoanalysis. On the mistaken premise that this is a variety of costoclavicular compression, operative procedures have been performed on the thoracic outlet. Among these are division of fibrous bands, scalenotomy, and removal of cervical ribs.

Recent studies substantiate the concept that this syndrome is in actual practice a symptom of compression of the median nerve at the wrist and that it is definitely related to the better known tardy median palsy. Division of the transverse carpal ligament at the wrist has given immediate and permanent relief.

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